NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED et al., Plaintiffs, v. NORWICH PHARMACEUTICALS, INC. et al., Defendants.	**Civil Action No. 20-8966 (SRC)** **OPINION**

CHESLER, District Judge

INTRODUCTION

Plaintiffs Takeda Pharmaceutical Company Limited and Takeda Pharmaceuticals U.S.A. Inc. (collectively, "Takeda") bring this action for patent infringement against Defendant Norwich Pharmaceuticals, Inc. ("Norwich.") This case concerns patents related to the pharmaceutical product Vyvanse®. Norwich is a pharmaceutical company which filed ANDA No. 214547 to produce a generic version of this pharmaceutical product. Takeda owns U.S. Patent No. 7,655,630 ("the '630 patent"), U.S. Patent No. 7,662,787 ("the '787 patent"), U.S. Patent No. 7,687,466 ("the '466 patent"), U.S. Patent No. 7,105,486 ("the '486 patent"), U.S. Patent No. 7,678,770 ("the '770 patent"), U.S. Patent No. 7,671,031 ("the '031 patent"), U.S. Patent No. 7,223,735 ("the '735 patent"), U.S. Patent No. 7,700,561 ("the '561 patent"), and U.S. Patent No. 7, 671,030 ("the '030 patent"). All patents are listed in the Orange Book as

protecting Plaintiffs' Vyvanse® l-lysine-d-amphetamine ("LDX") dimesylate product. Takeda asserts claims 1 and 4 of the '630 patent, claim 2 of the '787 patent, claim 14 of the '466 patent, claim 4 of the '486 patent, claims 5 and 10 of the '770 patent, claim 7 of the '031 patent, claim 12 of the '735 patent, claims 1, 6, and 9 of the '561 patent, and claims 4 and 25 of the '030 patent. Norwich contends that the asserted patent claims are invalid, pursuant to 35 U.S.C. §§ 102 or 103, or the enablement requirement of 35 U.S.C. § 112. The parties have stipulated to infringement of the claims at issue. A bench trial on patent validity was held for 3 days, beginning on November 7, 2022, and ending on November 9, 2022. Upon hearing the evidence presented at trial, this Court finds that Norwich has failed to prove that the claims at issue are invalid.

STIPULATED FACTS

The parties stipulated to the following facts in the Final Pretrial Order ("FPO"):

2. The patents-in-suit were previously litigated in the District of New Jersey: Shire LLC et al. v. Amneal Pharmaceuticals, LLC et al., Civil Action No. 2:11-03781-SRC-CLW (consolidated).

9. Norwich does not contest personal jurisdiction in this Court for the purposes of this action.

10. Norwich does not contest that venue is proper in this Court under 28 U.S.C. §§ 1391(b) and (c), and § 1400(b) for purposes of this action.

12. L-lysine-d-amphetamine may also be referred to as lisdexamfetamine or lisdexamphetamine.

15. Takeda Pharmaceutical Company Limited has been assigned, and currently holds all rights, title and interest in and to the Patents-in-Suit.

48. The '770 patent was filed on August 29, 2008 as Application No. 12/201,739, which was a continuation of Application No. 11/400,304, filed on April 10, 2006, which is a continuation-in-part of Application No. 10/857,619, filed on June 1, 2004 (now U.S. Patent No. 7,223,735); Application No. 11/400,304 is also a

continuation-in-part of Application No. 10/858,526, filed on June 1, 2004, (now U.S. Patent No. 7,105,486), which is a continuation-in-part of Application No. PCT/US03/05525, filed on February 24, 2003.

90. Norwich sent a letter dated June 3, 2020 to Shire Development LLC and Shire LLC providing notification that the Norwich ANDA contains certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "paragraph IV certification") with regard to the patents-in-suit.

115. L-lysine-d-amphetamine dimesylate is a prodrug of d-amphetamine. That is, it is biologically inactive until it is converted in the body to d-amphetamine.

THE ISSUES FOR TRIAL

1. Has Defendant proven, by clear and convincing evidence, that claims 1 and 4 of the '630 patent, claim 2 of the '787 patent, claim 14 of the '466 patent, claim 4 of the '486 patent, claims 5 and 10 of the '770 patent, claim 7 of the '031 patent, claim 12 of the '735 patent, claims 1, 6, and 9 of the '561 patent, and claims 4 and 25 of the '030 patent are invalid as obvious, pursuant to 35 U.S.C. § 103?

2. Has Defendant proven, by clear and convincing evidence, that claims 5 and 10 of the '770 patent, claim 12 of the '735 patent, claims 1, 6, and 9 of the '561 patent, claim 1 of the '630 patent, claim 4 of the '486 patent, claim 7 of the '031 patent, and claims 4 and 25 of the '030 patent are invalid as not enabled, pursuant to 35 U.S.C. § 112 ¶ 1?

3. Has Defendant proven, by clear and convincing evidence, that claim 10 of the '770 patent is invalid as anticipated, pursuant to 35 U.S.C. § 102?

THE EVIDENCE AT TRIAL

What follows are selected summaries of the testimony of the witnesses appearing in Court at trial:

A. Testimony of John Peter Mallamo

Dr. Mallamo was qualified as an expert witness in the field of medicinal chemistry, including prodrugs and drug formulation. (Tr. 50:24-51:2.) Dr. Mallamo stated that he based his opinions on the state of the art as of May 29, 2003. (Tr. 55:1-2.) Balant, published in 1990, teaches the use of prodrugs to modify properties of a compound, including modification of the pharmacokinetics to improve absorption, distribution, metabolism, and excretion. (Tr. 55:11-14, 56:21-25.) Adrian Albert coined the term, "prodrug," in 1958. (Tr. 57:5.) Today, we will speak about an amine-containing drug and an L-amino acid promoiety, which are combined to create a prodrug. (Tr. 57:12-17.) As to how forming a prodrug affects the pharmacokinetics of the drug: "So initially you have to design these materials so that the in vivo liability is sufficient to produce a therapeutic, the effective amount of the drug so the active moiety will release at a rate which would ensure that it's being produced in the bloodstream at a therapeutic level." (Tr. 57:21-58:2.) The prodrug and the carrier molecule should be nontoxic; relatively safe moieties are the 20 amino acids. (Tr. 58:3-6.) The prodrug should improve on the performance of the drug. (Tr. 58:7-11.) When you make a prodrug that is regenerated by an enzyme, enzymes perform their functions at a rate; you will have the time-dependent release of the drug through enzymatic catalysis, affecting the duration of effect. (Tr. 58:12-18.) We look in the PDR for drugs useful in treating ADHD, and we look for drugs containing dextroamphetamine sulfate. (Tr. 59:19-60:3.) There are immediate release, delayed release, and extended release formulations. (Tr. 60:8-11.) Amphetamine and amphetamine sulfate have a number of side effects, and we are going to focus on euphoria; it is a Schedule II substance with a black box warning about dependency and abuse potential. (Tr. 60:16-20.) Patrick is a medicinal

chemistry textbook published in 2001 which discloses medicinal chemistry design strategies. (Tr. 61:5-22.) Prodrugs are useful for problems such as permeability, drug toxicity, and flavor masking. (Tr. 62:2-4.) Dr. Mallamo said that he relied on the section entitled, Prodrugs: masking, drug toxicity, and side effects. (Tr. 62:14-17.) A POSA would have found particularly relevant the prodrug example on page 449-30, which discusses LDZ, a prodrug of diazepam, designed to avoid a drowsiness effect associated with rapid onset that occurs with diazepam when administered by normal routes of administration. (Tr. 64:25-63:9.) Patrick shows the LDZ prodrug formed from diazepam and an L-series amino acid. (Tr. 68:21-69:2.) The prodrug exhibits tempered conversion into the active compound by in vivo hydrolysis: an aminopeptidase hydrolizes off the lysine moiety, and the resulting amine spontaneously cyclizes to diazepam, as shown in Patrick figure 10.39. (Tr. 70:11-71:1.) A POSA would know that, similar to d-amphetamine, diazepam has one amine group available with which an amino acid could react to form an amide prodrug. (Tr. 71:16-25.) A POSA would know that the amide linkage between the amide group and the lysine is driven by the lack of available derivatizable functional groups on diazepam and the available primary amine. (Tr. 72:25-73:5.) As with d-amphetamine, a POSA would know that an amide linkage is the most straightforward reaction with the carboxylic acid functional group on the lysine. (Tr. 73:6-9.) A POSA would expect that conjugating l-lysine to d-amphetamine would similarly hydrolyse off the lysine moiety at a rate-dependent manner to release the active, thus reducing the initial plasma level spikes of d-amphetamine. (Tr. 73:15-21.)

U.S. Patent No. 3,843,796 issued in 1974 to Miller. (Tr. 74:8-9.) Miller discloses the application of an amino acid to an antihypertensive agent, metaraminol, so that it will not

produce a rapid-onset side effect, a potentially fatal hypertensive event. (Tr. 74:17-24.) Miller attempts to solve the problem of too-rapid release of metaraminol by creating a prodrug with a number of L-series amino acids. (Tr. 76:3-14.) Metaraminol has a free amino group which joins to the carboxylic acid group of l-lysine to create an amide bond which would diminish its activity. (Tr. 76:25-77:5.) When an enzyme releases the lysine, the drug is freed and can act as it normally would, but in a more rate-controlled manner. (Tr. 77:6-8.) Miller Example 5 discloses the process of synthesizing a prodrug with l-lysine. (Tr. 77:20-24.) The lysine is masked to prepare it to bond with the metaraminol. (Tr. 78:5-15.) It is true that Example 5 does not result in the prodrug compound, because the end result compound has protecting groups attached, but a POSA would have known how to remove them to result in the prodrug. (Tr. 79:3-80:2.)

A POSA looking to develop a new ADHD medication would look for a good starting point, a lead molecule, which here is d-amphetamine, "a very commonly used ADHD component." (Tr. 81:2-8.) The utility of d-amphetamine is limited by euphoria, which causes abuse of the drug; if you can eliminate that, you improve the products that contain d-amphetamine. (Tr. 81:4-14.) At the time, while some amphetamine drugs contained both d-amphetamine and l-amphetamine, all amphetamine drugs contained d-amphetamine, which is four times more potent than l-amphetamine. (Tr. 82:16-83:4.) The art contained other stimulant treatments for ADHD, but a POSA would not have been motivated to choose any as a lead compound. (Tr. 85:22-86:3.) The literature points to the class of stimulant medications, and the two most-used drugs were d-amphetamine and methylphenidate, and pemoline was found to cause liver failure. (Tr. 88:7-23.) At the time, there was growing interest in extended-

release d-amphetamine formulations, which was an attempt to alleviate the drug's abusability. (Tr. 89:11-15.) With methylphenidate, it would be hard to be certain that a conjugate would be easily bioreversible and chemically stable, and its ester group would have to be masked. (Tr. 90:5-21.) Nonstimulant treatments were less used and less efficacious, so not very interesting. (Tr. 91:1-18.) Knowledge of the abuse potential of d-amphetamine would have motivated a POSA to modify it. (Tr. 92:1-4.) The PDR discloses that the euphoric side effect drives the abuse. (Tr. 92:13-14.) A POSA would understand that euphoria is caused by the rapid onset of the drug, the initial high plasma concentrations in immediate release formulations. (Tr. 93:5-10.)

Patrick teaches that his diazepam prodrug avoids a drowsiness side effect associated with high initial plasma levels of diazepam. (Tr. 93:21-94:1.) Bundgaard teaches that bioreversibility is important in a prodrug, and that the most common prodrugs are those requiring hydrolytic cleavage mediated by enzyme catalysis. (Tr. 94:17-95:3.) The Piccariello and Kirk publication, published September 4, 2003, teaches that prodrugs will reduce the initial spike in plasma levels, that prodrugs would avoid the euphoric effect associated with the spike, and that d-amphetamine would be suitable for a prodrug. (Tr. 95:14-97:4.) The crushing of an extended release formulation allows for rapid release of the active, so a POSA would not have selected an abuse-resistant formulation approach over a prodrug approach. (Tr. 97:17-99:2.) Biel says that d-amphetamine is a ready target for extensive molecular modification. (Tr. 100:16-19.) Patrick teaches that the amino group of diazepam can be coupled with l-lysine and then liberated by an enzyme, and the same can be done with d-amphetamine. (Tr. 101:16-102:10.) L-lysine is present in food and is known to be safe and nontoxic. (Tr. 102:24-103:2.)

L-lysine is on the GRAS list, which would have been important to a POSA choosing a promoiety for d-amphetamine. (Tr. 103:5-25.) Both Patrick and Miller teach using l-lysine prodrugs to sustain release and suppress the initial-onset effect. (Tr. 105:14-22.) Hutchinson uses l-lysine prodrugs to improve solubility, and Piccariello teaches that d-amphetamine can be inactivated by binding it with a moiety. (Tr. 105:23-106:7.) Hutchinson says that this strategy is similar to that used by Pochopin. (Tr. 107:1-5.)

Patrick teaches that an amino peptidase enzyme hydrolyses off the lysine from the diazepam prodrug, and Miller proposes various families of enzymes, all present in the body. (Tr. 112:19-113:6.) The twenty amino acids can be put into four buckets based on physical properties, with histidine, arginine and lysine in the group of amino acids which are polar but positively charged at physiological pH. (Tr. 114:18-115:4.) Lysine has roughly the same pKa number of d-amphetamine, around ten, so they match perfectly. (Tr. 115:13-17.) Pochopin 1994 discloses an l-lysine prodrug. (Tr. 116:3-23.) A POSA would have safety concerns about using a d-series amino acid, which is a nonnatural amino acid in the body, so enzymes tend to recognize it less, and a prodrug might not cleave or might cleave at a much slower rate. (Tr. 117:6-13.) In addition to an amide bond, d-amphetamine also has a hydroxyl group that could be used to create an ester bond with a promoiety. (Tr. 117:14-18.) Pochopin 1995 teaches that amide bonds are more stable than ester bonds, so amide prodrugs are more stable than ester prodrugs. (Tr. 117:21-118:14.) A POSA would not need express instructions on how to isolate LDX from a crude reaction mixture. (Tr. 118:15-24.) Both Miller and Patrick show success in forming a lysine prodrug, and d-amphetamine has similar structural characteristics to the drugs they were interested in: an available primary amine group. (Tr. 120:16-21.)

LDX "has with it an associated side effect that the literature is telling us that is addressable through this technology. . . and that side effect is a single limiting principal factor in the medical utility of this drug." (Tr. 123:18-22.) Of the 20 natural amino acids, l-lysine would have been obvious to try. (Tr. 125:22-126:1.) "Enzymatic hydrolysis is known to be a rate-limiting step that results in reduction of rapid onset of the drug through a rate-controlled release." (Tr. 127:11-13.) Calculating a dosage range for LDX is a straightforward two-step calculation, starting from the PDR disclosure of the range of 5 to 40 mg of d-amphetamine sulfate. (Tr. 129:4-24.) A formulator would formulate an oral formulation using very common excipients: microcrystalline cellulose as a binder, croscarmellose sodium as a disintegrant, and magnesium stearate as a lubricant, based on the information in the Handbook of Pharmaceutical Excipients. (Tr. 135:22-138:17.) A POSA would have had a reasonable expectation of success in making such a formulation because "there is no reason to suspect these would not work." (Tr. 138:18-22.)

On cross-examination, Dr. Mallamo agreed that he was not an expert in ADHD and that he had never been involved with an attempt to reduce abusability by formulation. (Tr. 146:15-20.) LDX is not found in the prior art. (Tr. 149:1-4.) A motivation to modify d-amphetamine was to solve its problem of abusability, and neither Miller nor Patrick discuss reducing abuse. (Tr. 149:5-150:1.) Patrick does not disclose the T_{max} or C_{max} for diazepam, nor say by how much LDZ reduced initial plasma concentrations compared to diazepam. (Tr. 154:12-155:5.) Patrick does not disclose how long the cyclization process takes, nor how long it takes to cleave the l-lysine group in plasma. (Tr. 155:6-14.) Miller does not disclose any plasma concentration measurements, or reduction in C_{max}, or change in T_{max}. (Tr. 157:24-158:7.)

Formula II in Miller does not disclose compounds with free lysine as preferred. (Tr. 161:10-12.) The enzyme that cleaves LDX is still unknown. (Tr. 166:19-21.) A POSA would have reasonably expected that the enzyme trypsin would cleave l-lysine from LDX. (Tr. 167:14-18.) Subsequent research has shown that trypsin does not do so. (Tr. 167:19-25.) The Biel 1975 reference uses both D- and DL-amino acids. (Tr. 169:8-15.) There is no reason to avoid d-lysine in a prodrug. (Tr. 169:22-24.) A d-lysine prodrug would have a slower rate of release than a l-lysine prodrug. (Tr. 169:25-170:25.) There could be a prodrug that results in a shorter T_{max} and a higher C_{max} compared to amphetamine. (Tr. 172:11-13.) An amphetamine prodrug that released amphetamine very quickly might be a more abusable drug. (Tr. 174:17-19.) To assess whether an intact amphetamine prodrug was inactive, a POSA would need to run a test. (Tr. 175:18-176:1.) Dr. Mallamo agreed that, in his expert report, he relied on Dr. Sloan's opinion that the water content of LDX would be 7.3%, but in his testimony today, he switched from 7.3% to 3.8%. (Tr. 178:16-179:3.)

B. Deposition Testimony of James C. Ermer

Mr. Ermer said that he was senior director of clinical pharmacology and pharmacokinetics at Shire. (Tr. 185:1-3.) We were never certain that LDX would cleave off the molecule in humans. (Tr. 187:23-25.) It was surprising that red blood cells cleaved LDX. (Tr. 188:10-13.)

C. Deposition Testimony of Robert Oberlender

Mr. Oberlender said that he was hired at New River in August of 2000. (Tr. 194:1-3.) When we tested LDX, it had a decreased C_{max} relative to amphetamine, and it had a nice plateau over two to four hours, which was exactly what we were looking for. (Tr. 194:19-195:4.) It is

convenient to do a synthesis of LDX and end up with a salt form because it is easier to crystallize in most cases. (Tr. 196:18-197:3.) The amphetamine conjugates had a real problem with hygroscopicity, the tendency of a molecule to pull water out of the air; this was a particular problem with LDX. (Tr. 197:18-24.) I had trouble getting LDX to crystallize as a dihydrochloride and I tried several different crystallization techniques. (Tr. 197:24-198:1.) We made the sulfate to see if it was less hygroscopic. (Tr. 198:5-7.)

D. Deposition Testimony of Christopher Verbicky

Mr. Verbicky said that he began work for Albany Molecular in 2000 and was a senior research scientist in 2003. (Tr. 199:17-24.) The synthesis of the dihydrochloride salt of LDX produced a very hygroscopic foam, which was less than ideal for scaling up. (Tr. 201:1-8.) Because the dihydrochloride salts became hygroscopic, we decided to explore different salts. (Tr. 202:4-14.) On July 25, 2003, we reported the first formation of the dimesylate salt. (Tr. 203:6-16.)

E. Deposition Testimony of James Moncrief

Dr. Moncrief stated that he began working at New River Pharmaceuticals in 2000, and he was a senior scientist when Shire acquired New River. (Tr. 205:7-17.) He recalled testing the dimesylate, sulfate, hydrochloride, and disulfate salts of LDX. (Tr. 205:18-206:1.) The assays were done after the product was in the bloodstream and no longer a salt, so the salt form is irrelevant at that point. (Tr. 206:6-14.)

F. Testimony of Kenneth B. Sloan

Dr. Sloan was admitted as an expert in the fields of organic and medicinal chemistry, including selection of salt forms of pharmaceuticals. (Tr. 211:12-23.) For a POSA researching

a new drug compound as of May 29, 2003, it would have been very common to investigate salt forms of the drug. (Tr. 219:16-21.) Morris teaches a salt-selection method. (Tr. 221:11-25.) There were other approaches to salt screens as of the priority date, and it was routine at that time. (Tr. 222:2-8.) A POSA would have had a reasonable expectation of success in developing a pharmaceutically acceptable salt of LDX, and the process would be straightforward. (Tr. 223:15-21.) LDX is weakly basic, and a POSA would want to form a salt using a stronger acid with a low pKa value. (Tr. 226:3-24.) Engel describes a salt selection process. (Tr. 229:6-23.) Smissman 1972 teaches the mesylate salt of amphetamine. (Tr. 238:11-239:6.) A POSA, as of the critical date, would have been motivated to pursue a mesylate salt form of LDX and would have had a reasonable expectation of success. (Tr. 240:23-241:5.) A POSA would have been motivated to make the dimesylate salt because it is easier to control the formation of that salt. (Tr. 241:15-19.) Residual water is undesirable with crystals because it can lead to instability; water getting inside the crystal can destroy the crystallinity. (Tr. 245:2-9.) Because it is almost impossible to synthesize a salt form that does not contain residual water, a POSA would have expected LDX dimesylate to contain residual water and would have been motivated to dry the compound to get the water content as low as possible. (Tr. 245:10-25.) The technique used most often to determine a drug's water content as of the priority date is called Karl Fischer titration. (Tr. 246:5-8.) Stahl teaches that mesylate salts have no tendency to form hydrates; a POSA would have expected a nonhydrated form to contain less than 3.8% water, based on a simple calculation. (Tr. 248:4-25.) A POSA would have been motivated to reduce the water content as low as possible to the range of .25% to 2%, with a reasonable expectation of success. (Tr. 249:5-250:19.)

To the extent that the claims at issue are nonobvious, they are not enabled. (Tr. 251:4-5.) There are thirteen patent applications of interest which fall into five groups: 1) no disclosure of salts; 2) disclosure of dihydrochloride salts and a method of synthesis; 3) second category plus disclosure of the dimesylate salt; 4) third category plus method of synthesis of dimesylate salt; and 5) disclosure only of dimesylate salt without method of synthesis. (Tr. 251:10-254:21.) Some of the claims at issue contain the phrase, "pharmaceutically acceptable salt," which can cover hundreds of salt forms. (Tr. 255:7-11.) The disclosures of the 13 applications are not sufficient to enable a POSA to make and use the full scope of these claims. (Tr. 255:17-21.) Dr. Verbicky's testimony showed that he and his team were unable to make the sulfate salt and could not isolate the hydrochloride salt because it was hygroscopic; it would take a lot of experimentation to make the full scope of pharmaceutically acceptable salts. (Tr. 257:5-258:8.) The report by Albany Molecular Research dated July 25, 2003 shows the difficulty they were having making these salt forms; developing every pharmaceutically acceptable salt of LDX would require a burdensome and time-consuming amount of experimentation. (Tr. 258:21-259:9.)

The claims with a mesylate salt limitation are not enabled because the inventors did not give any information about making a monomesylate salt, which is not the same as the method for making a dimesylate salt. (Tr. 259:19-260:10.) It is easy to make a dimesylate; when you try to synthesize a monomesylate by adding one equivalent of acid, you get a mixture of di-, mono-, and free base. (Tr. 260:8-18.) Claim 10 of the '770 patent is entitled to a priority date of August 29, 2008. (Tr. 264:11-16.) The 13 salt applications do not demonstrate that the inventors possessed the entire genus of pharmaceutically acceptable salts of LDX. (Tr. 263:14-

23.)

On cross-examination, Dr. Sloan stated that a POSA would routinely perform a salt screen, but he had never performed one. (Tr. 265:11-15.) The dimesylate salt would be obvious; he had never worked with a dimesylate salt. (Tr. 265:61-21.) Dr. Sloan agreed that his enablement opinion was in the alternative to his obviousness opinion. (Tr. 266:25-267:3.) Dr. Sloan was shown two patents on which he is sole inventor: 1) the first from 1980 with a claim stating, "nontoxic pharmaceutically acceptable salts thereof;" and 2) U.S. Patent No. 9,550,744, in which claim 5 states, "or a pharmaceutically or cosmetically acceptable salt thereof." (Tr. 267:17-271:11.) Dr. Sloan agreed that these patents did not explain how to make all the salts covered by the claims, nor how to make any salts; these claims in his patents were not enabled. (Tr. 267:17-271:11.) Dr. Sloan said that he has not told the PTO that these claims are not enabled. (Tr. 271:8-11.) The salt in the Engel reference he pointed out is a monomesylate monohydrate; in Dr. Sloan's analysis of the '630 patent, he said a POSA would use a nonhydrated form. (Tr. 271:24-272:16.) The water content for LDX dimesylate would be between .25% and 2%. (Tr. 272:19-22.) The water content for LDX dimesylate would be 3.8%, but not for the nonhydrated form that a POSA would use. (Tr. 273:7-12.) When trying to determine an appropriate LDX salt, he would look for diamines on LDX. (Tr. 273:23-274:2.) Engel does not have a diamine; only the Lin reference in his opening expert report had one, but Lin did not investigate a dimesylate salt. (Tr. 274:3-275:3.) Demonstrative DDX-302 expresses Dr. Sloan's opinion that the claims are obvious over Engel, in view of the opinions of Dr. Mallamo and other experts; Dr. Sloan did not rely on the PDR, Patrick or Miller references. (Tr. 275:13-276:8.) Dr. Sloan relied on Dr. Mallamo's opinions but has never spoken with him

and had not read any version of Dr. Mallamo's expert report before submitting Dr. Sloan's report; he was incorrect when he said at deposition that he had done so. (Tr. 276:9-277:21.) The starting point of Dr. Sloan's analysis was LDX free base, and he did not know about its hygroscopicity or need to have a change in solubility. (Tr. 277:22-278:19.) Increasing solubility can increase hygroscopicity; increased hygroscopicity can result in decreased stability. (Tr. 279:3-14.)

Dr. Sloan stated that he has over 30 patents that relate to prodrugs, and the work of most of his professional career has been on prodrugs. (Tr. 280:22-281:2.) He submitted a declaration that states that it is very difficult, unpredictable, and challenging to find a prodrug suitable to overcome a particular barrier. (Tr. 282:8-19.) It also stated: "for prodrugs that are cleaved enzymatically, there can be variability in the expression, location, and function of enzymes among different patient groups which causes further unpredictability of any prodrug candidate." (Tr. 282:23-283:6.) To make a salt from LDX free base, a POSA can add the appropriate acid, with a pharmaceutically acceptable counter ion, to make the salt. (Tr. 284:5-11.) The Bighley reference contains a flowchart for salt selection with this first step: determine the need for salt forms. (Tr. 284:14-285:17.) Bighley teaches that, at this first step, you should determine the viability of the neutral/free base compound, and Dr. Sloan agrees. (Tr. 285:21-286:7.) Dr. Sloan did not make that determination as to LDX. (Tr. 286:5-10.) As of the agreed-upon priority dates listed in paragraph 354 of his expert report, there was enablement as to the full scope of the claims. (Tr. 288:10-14.)

On redirect examination, Dr. Sloan stated that the declaration he submitted, which was the subject of cross-examination, concerned a method claim about water soluble prodrugs of l-

dopa. (Tr. 290:7-18.) He had opined in the declaration that to make every possible prodrug within the scope of the claim would be very burdensome. (Tr. 291:4-8.)

G. Testimony of Umesh Banakar

Dr. Banakar was admitted as an expert in the fields of pharmacokinetics, dosage form design, and drug product development and evaluation. (Tr. 349:4-8.) Dr. Banakar stated that he evaluated claim limitations involving pharmacokinetic ("PK") parameters, and relied on the opinions of Dr. Mallamo and Dr. Sloan. (Tr. 351:2-352:11.) The claimed values of the pharmacokinetic parameters are nothing but the result of the release of the drug, and "they are inherent to the administration of the immediate release formulation, and the inventors just claim the results." (Tr. 357:9-13.) Salts are irrelevant to this because the salt gets dissociated from the drug substance following administration. (Tr. 357:20-25.) Dr. Banakar stated that the PK parameters in claim 25 of the '030 patent correspond to the data in Tables 66 and 68. (Tr. 358:7-362:8.) The dosage form is an immediate release formulation and the formulation does not contribute to the inherent PK of the drug. (Tr. 363:10-20.) The PK parameters in claim 4 correspond to the data in Tables 65 and 67. (Tr. 364:22-366:5.) The PK parameters in claim 6 in the '561 patent correspond to the data in Table 72. (Tr. 366:8-368:23.) The PK parameters in claim 9 correspond to the data in Table 71. (Tr. 369:6-372:15.) In claim 12 of the '735 patent, the "limited bioavailability" and "sustained release" limitations reflect the results of administration of the drug through various routes, as shown in the specification; the inventors claimed their observations and results. (Tr. 372:17-378:25.) In claim 10 of the '770 patent, the limitation requiring therapeutic effects to occur from two hours to 12 hours after administration reflects the results shown in Example 35 and claims those results. (Tr. 379:15-382:10.) The

Krishnan and Moncrief reference states: "the pharmacokinetic profile of LDX is inherent to the chemical prodrug nature. . ." (Tr. 383:4-24.) A poster presentation by a group including one inventor, Krishnan, states: "the pharmacokinetic profile of LDX is inherent to its chemical prodrug nature. . ." (Tr. 384:16-25.) The use of prodrug technology resulted predictably in decreased C_{max} and increased T_{max}. (Tr. 385:8-13.)

On cross-examination, Dr. Banakar agreed that, at his deposition, he stated that he did not know who Drs. Mallamo and Sloan are, and he testified today that he relied on the opinions of both. (Tr. 388:20-390:25.) He stated that he relied on the opinions of Dr. Kaye, and that he has not heard his opinions. (Tr. 391:14-23.) His understanding of the opinions of these three other experts came from counsel for Norwich. (Tr. 392:8-12.) The six PK parameters in claim 4 of the '030 patent are for amphetamine. (Tr. 394:24-395:4.) Dr. Banakar agreed that, at his deposition, he said that the PK parameters are inherent to LDX itself. (Tr. 395:5-19.) Generally, he agreed with Dr. Taft that pharmacokinetics can be adjusted by factors other than the active ingredient. (Tr. 396:13-16.) He does not disagree with Dr. Sloan's testimony that a salt could impact bioavailability. (Tr. 396:17-21.) Every immediate release pharmaceutically acceptable salt of LDX will result in the same AUC. (Tr. 397:7-12.) Different salts may have different solubilities. (Tr. 398:6-9.) Lower dissolution results in a lower C_{max} and lower AUC compared to the same amount of prodrug formulated with a higher solubility salt. (Tr. 398:13-17.) It is possible that LDX mesylate would have a higher C_{max}, higher absorption rate, and higher dissolution rate than other salts. (Tr. 398:24-400:1.) Dr. Banakar agreed that, in his rebuttal expert report, he said that, because the mesylate salt is more soluble, a POSA would expect it to have a higher dissolution rate and absorption rate than other salts. (Tr. 400:4-16.)

The dosage form (solid vs. solution) can affect AUC. (Tr. 401:15-22.) Dr. Banakar agreed that "excipients chosen for a formulation can exert a profound influence on a finished product's bioavailability profile." (Tr. 402:5-10.) The therapeutic effects limitations in claim 10 of the '770 patent are inherent to LDX. (Tr. 404:5-8.) At his deposition, he said that he could not determine whether the PK parameters of claims 4 and 25 of the '030 patent were inherent to the Norwich ANDA LDX products. (Tr. 405:4-24.)

The Court asked Dr. Banakar why, if the ANDA product is the same product as the claimed LDX, and the claimed LDX has an inherent PK profile, he said he could not determine whether Norwich's LDX product would meet the limitations for the PK parameters. (Tr. 411:2-412:1.) Dr. Banakar agreed that, logically, Norwich's LDX product would have to infringe the PK parameter limitations. (Tr. 412:2-5.)

H. Testimony of Neil Kaye

Dr. Kaye was admitted as an expert in the treatment of ADHD. (Tr. 414:22-415:1.) Dr. Kaye stated that d-amphetamine compounds are Schedule II drugs and highly addictive and abusable, and must be prescribed in limited quantities. (Tr. 414:11-14.) The method of treatment claims are claim 4 of the '486 patent, claim 7 of the '031 patent, and claims 5 and 10 of the '770 patent; the method of dosage claims are claims 1, 6, and 9 of the '561 patent and claims 4 and 25 of the '030 patent. (Tr. 415:23-416:3.) Dr. Kaye relied on the opinions of Drs. Sloan and Mallamo as to aspects of the claims not involving a method of treatment. (Tr. 417:12-418:1.) The PDR taught that d-amphetamine was a safe and effective treatment for ADHD. (Tr. 418:15-18.) The PDR states that the typical daily dose range for Dexedrine (d-amphetamine sulfate) is 5 to 40 mg. (Tr. 419:2-18.) A POSA could do the routine calculation

to determine the LDX dosage for equivalence to this range. (Tr. 422:9-19.) Given this, a POSA would have been motivated to treat a patient with ADHD by orally administering an effective amount of LDX mesylate with a reasonable expectation of success. (Tr. 423:14-24.) The method of treatment in claim 7 of the '031 patent would have been obvious to a POSA. (Tr. 426:8-13.) If the priority date of claim 10 of the '770 patent is August 29, 2008, it is anticipated by the '995 Publication, dated February 22, 2007. (Tr. 437:19-438:14.) Example 34 of the '995 Publication discloses a pediatric study of single-dose oral administration of LDX dimesylate using dosages of 30, 50, and 70 mg. (Tr. 439:1-4.) Example 35 discloses that the significant effects of LDX occurred within 2 hours of the morning dose and continued through the point twelve hours after the morning dose. (Tr. 441:7-14.) Claim 10 of the '770 patent also would have been obvious in view of the '995 Publication. (Tr. 441:18-24.)

On cross-examination, Dr. Kaye was shown patent application no. 11/400,304 and asked if, hypothetically, this application was identical to the '995 Publication, his testimony about the '995 Publication would equally apply to the application; Dr. Kaye said it would. (Tr. 443:1-444:18.)

I. Testimony of James McGough

Dr. McGough was admitted as an expert in psychopharmacology, pharmacotherapies, and the development of pharmacotherapies for ADHD. (Tr. 460:17-25.) Dr. McGough stated that he was involved in the development of new medications for the treatment of ADHD in the late 1990s and early 2000s. (Tr. 464:1-10.) At that time, the medications required redosing after four hours, which meant a lot of pills in schools, and there was real concern about illicit diversion of those medications. (Tr. 464:11-25.) There were also ongoing issues about actual

abuse of the medications, which could easily be crushed and snorted and used like cocaine. (Tr. 465:1-4.) There began to be introduction of extended release medications, like Concerta. (Tr. 465:7-15.) The amphetamines were the dominant medication used until the 1960s, when methylphenidate was developed as a response to concern about abuse of amphetamines; by the 1990s, methylphenidate was about 95% of prescriptions. (Tr. 465:18-466:4.) D-amphetamine was a small amount of prescriptions at that time and has remained very minimal. (Tr. 466:5-7.) At that time, the field looked to nonstimulant treatments to reduce abuse potential, and a lot of effort was put into that. (Tr. 467:1-10.) When stimulants are crushed, snorted, or injected, they go into the body so quickly that it is like cocaine, and are very abusable. (Tr. 468:15-21.) With Vyvanse®, release of the amphetamine is dependent on an enzymatic process that limits the amount of amphetamine that can get into the body, thus mitigating the risk of abuse. (Tr. 468:25-469:11.) Dr. McGough said that he was involved in the development of Vyvanse®, but did not receive any direct payments from the pharmaceutical companies. (Tr. 469:17-471:2.) Vyvanse® addressed the needs of people with ADHD for a single, morning, extended release, reliable ADHD medication with decreased risk of abuse. (Tr. 471:17-23.) The method and dosage claims at issue would not have been obvious to the POSA. (Tr. 473:1-17.) "Absent testing, a POSA would not have been motivated to use the claimed dose ranges because the rate and extent of release of d-amphetamine from the prodrug was unknown." (Tr. 473:18-20.) "Prodrugs themselves can be unpredictable. It can be unpredictable if it is truly inactive when ingested. It is unpredictable as to whether it will be successfully cleaved and the manner in which it will be cleaved." (Tr. 476:15-19.)

Table 46 in the '486 patent shows the extensive research conducted to determine the

proper d-amphetamine prodrug candidate. (Tr. 477:6-478:3.) The "K-amp" compound is LDX, and 98% gets into the body when administered orally, but barely any gets in if it's snorted and 3% intravenously. (Tr. 478:25-479:7.) For the serine amphetamine prodrug, 79% gets into the body when administered orally, and 76% if you snort it. (Tr. 479:8-14.) Depending on the amino acid used in the prodrug, there is great variation in terms of what gets taken in when taken orally versus intranasally. (Tr. 479:15-18.) This shows that one would not know that lysine is the proper prodrug to use. (Tr. 479:25-480:2.) Absent data like this, an amphetamine prodrug would not be predictable. (Tr. 480:10-18.) For treating ADHD, it is important to have rapid enough intake of the medication to give early control of symptoms, but not so rapid as to make you high, and you need sustained release over time for symptom control over an extended period. (Tr. 481:23-482:3.) Many prodrugs have the characteristic of Valcyte: they must pass through the liver to get transformed into the active medication. (Tr. 483:7-15.) Dr. Kaye's opinion that the dosage ranges are the product of routine calculation is based on hindsight, since before testing you would not know how much amphetamine will come off the prodrug. (Tr. 485:2-20.) As Dr. Banakar said, the PK activity of the molecule is in part dependent on the formulation. (Tr. 486:2-5.) You need to know the pattern of blood concentration over time, which you will not know without testing. (Tr. 486:12-15.)

There had been two big problems with the prior art use of stimulant treatments, which Vyvanse® addressed: 1) illicit diversion, which was solved to some extent by an extended release version; and 2) the ability to abuse the compound by crushing it, snorting it, and injecting it. (Tr. 491:6-17.) Vyvanse® satisfied the long-felt need for a stimulant with reduced abuse potential. (Tr. 491:18-20.) Two research studies showed that drug abusers like it less. (Tr.

493:1-494:18.) The Vyvanse® label carries a black box warning of the risk for abuse and dependency. (Tr. 496:17-497:3.) The Ermer 2011 study compared oral to intranasal administration and showed equivalent bioavailability of d-amphetamine; the uptake and distribution of the active did not differ. (Tr. 497:17-498:25.) It was surprising and unexpected that an amphetamine compound could be released in a manner effective to treat ADHD but with less abuse potential. (Tr. 499:5-9.) At the time of development, there were other extended release stimulants, but Vyvanse® was the first to demonstrate benefit beyond 12 hours, thus satisfying the need for stimulants with longer duration of effect. (Tr. 500:3-18.) The Wigal study demonstrated effects in children up to 13 hours. (Tr. 501:5-24.) The Giblin and Adler studies showed that LDX does not contribute to sleep disturbances. (Tr. 504:4-505:1.) Dr. McGough did a study on Adderall XR and found high inter-person pharmacokinetic variability; Biederman compared LDX and Adderall XR and found LDX showed much lower interpatient pharmacokinetic variability, demonstrating that Vyvanse® satisfied the need for stimulants with reduced pharmacokinetic variability. (Tr. 508:2-510:7.) The art showed initial skepticism about Vyvanse®, but a 2011 publication of The Medical Letter shows praise for the long duration of action, and Goodman's review praised its low interpatient variability for key pharmacokinetic parameters. (Tr. 512:10-515:10.) Faraone's review cites three benefits of LDX: high efficacy effect size, reduced potential for abuse-related liking, and low interpatient variability in pharmacokinetic parameters. (Tr. 516:6-11.) Elbe wrote that LDX significantly reduces the likelihood of abuse by stimulant-seeking abusers. (Tr. 516:13-18.)

The face page of the '770 patent states that it is a continuation of the '304 application, and claims benefit to the '548 provisional application. (Tr. 517:22-518:3.) The '955

Publication simply published the '304 application and does not differ from it in any way. (Tr. 518:14-16.) Claim 9 and Example 34 of the '548 application disclose the efficacy of LDX dimesylate for the treatment of ADHD in children ages 6 to 12, with a 12-hour duration of action. (Tr. 518:21-519:20.) The '304 application also disclosed this. (Tr. 520:3-22.)

Dr. Mallamo misunderstood AACAP 1997, which referred to increasing use of amphetamines, but it was referring to mixed amphetamine salts like Adderall XR (25% amphetamine l-isomer), not Dexedrine or d-amphetamine. (Tr. 521:6-522:14.)

On cross-examination, Dr. McGough stated that the principal of titration is that you find the appropriate level for the patient. (Tr. 523:12-16.) A POSA would do this as standard clinical practice. (Tr. 524:10-22.) Dr. McGough, in his clinical practice, has no preference between methylphenidate and amphetamine treatment, but many factors come into play, including insurance coverage. (Tr. 529:7-530:1.) Titration is done within FDA-approved ranges demonstrated in clinical studies; absent such data, no POSA would dare to titrate because you would not know where to begin. (Tr. 534:6-18.) Vyvanse® can be abused, but it is reduced compared to others. (Tr. 535:2-3.) The Cochrane review did a meta-analysis of studies of the use of amphetamines for ADHD and concluded that they found no evidence that supports one amphetamine derivative over another or reveals differences between long-acting and short-acting amphetamine preparations. (Tr. 538:9-529:17.)

On redirect examination, Dr. McGough said that the statement in the Cochrane review about there being no evidence that one treatment is better than another means that nobody has done the study which shows that. (Tr. 540:17-541:13.)

J. Deposition testimony of Sivawosh Moghaddam

Dr. Moghaddam stated that he was vice-president of analytical services and research and development for Alvogen. (Tr. 548:25-549:3.) He worked on the ANDA LDX dismesylate product for Norwich. (Tr. 549:22-24.) The original idea was to develop an alternate salt to LDX dimesylate. (Tr. 550:5-6.) At some point, Norwich decided not to pursue alternate salts, but to pursue LDX dimesylate. (Tr. 550:20-25.) A different salt could have different solubility and stability; you cannot predict whether the pharmacokinetics will be the same or different. (Tr. 552:7-24.) AMRI worked on salt selection, screening 29 acids at two stoichiometry levels against ten solvents. (Tr. 553:4-554:5.) After the screening, three salts were identified: the monomesylate, the dimesylate, and the monocyclamate. (Tr. 554:6-16.) Various salts had been found to have stability issues. (Tr. 557:19-558:4.) At one point in the development of LDX capsules, the API was found to have poor flow, which would pose challenges in manufacturing. (Tr. 559:13-560:8.) The FDA requires excipient compatibility studies to show that excipients are compatible with the API, which is very difficult to predict. (Tr. 562:4-14.) We need to perform dissolution testing; it's difficult to predict those results. (Tr. 562:15-563:6.) Mesylates have been associated with genotoxic impurities. (Tr. 563:7-15.)

K. Deposition testimony of Paul Fackler

Dr. Fackler stated that he is employed by Alvogen and led the clinical R&D group which oversaw the bioequivalence studies for the Norwich LDX dimesylate ANDA. (Tr. 565:8-566:5.) Dr. Fackler stated that he could not predict in vivo performance from merely looking at a molecule. (Tr. 567:3-5.) While you can predict rate and extent of absorption for some molecules, but for most, including LDX dimesylate, you must run tests. (Tr. 567:15-23.)

Choice of excipients can affect the AUC. (Tr. 567:24-568:1.) Method of manufacture and salt selected can affect the PK properties. (Tr. 568:2-7.) One cannot know or predict where in the body a prodrug molecule would be hydrolysed just by looking the molecule. (Tr. 569:6-13.) The C_{max} and AUC of LDX are not inherent to LDX and the formulation affects them. (Tr. 569:20-570:8.) Before testing, one cannot predict bioequivalence of a generic product. (Tr. 572:1-7.) If the reference product and the generic product have different solubility rates with the same active, the PK profiles can be different. (Tr. 572:14-24.) Particle size distribution (surface area of the API) can differ; ordinarily, a higher surface area can mean a faster dissolution rate, which results in different PK parameters. (Tr. 573:3-13.)

L. Deposition testimony of Travis Clark Mickle

Dr. Mickle stated that he was president and CEO of KemPharm; he previously worked for New River Pharmaceuticals. (Tr. 574:24-575:11.) At the beginning of developing the prodrug, they considered many molecules as a promoiety, not just single amino acids: "anything really that existed in nature." (Tr. 576:10-18.) They learned that every prodrug is unique, and that you cannot predict the behavior of the prodrug from knowing the amino acid attached to it: "it's entirely an empirical process." (Tr. 577:10-15.) Lysine was found to be a good choice because of the PK profile of released amphetamine in animals and later in humans, and the molecules seemed to be stable to chemical hydrolysis. (Tr. 578:22-579:12.) Some amide bonds are weak and break apart easily; you have to test to find out if that bond will endure what you or an abuser will put it through. (Tr. 579:15-21.) Lysine was one of the last amino acids we tested because it was hard to prepare, compared to other amino acids, and it was hygroscopic. (Tr. 580:5-9.)

M. Deposition testimony of Kristie Whitehouse

Ms. Whitehouse stated that she worked for Takeda and is director of consumer marketing for Vyvanse®. Vyvanse® is a commercial success, a blockbuster with over a billion dollars in revenue. (Tr. 586:5-13.) Its success is driven by its efficacy and safety profile. (Tr. 586:17-22.)

N. Testimony of Alexander Klibanov

Dr. Klibanov stated that he was professor emeritus of chemistry and bioengineering at MIT and a consultant in pharmaceutical sciences, and founded six pharmaceutical companies of his own. (Tr. 639:7-640:3.) Dr. Klibanov was admitted as an expert in pharmaceutical drug development. (Tr. 640:4-7.) "Prodrugs were, as of 2003 and, indeed, still are very difficult, unpredictable, and challenging." (Tr. 641:21-23.) Patrick refers to many promoieties, not just the one Dr. Mallamo selected. (Tr. 644:19-22.) Patrick contains a section titled, "Prodrugs masking drug toxicity and side effects," which begins with aspirin. (Tr. 645:17-22.) Patrick teaches about the prodrug LDZ, in which l-lysine is linked to a precursor of diazepam, made possible because the 8-member ring of diazepam is opened up. (Tr. 646:14-647:1.) Such an approach cannot work for d-amphetamine because it has no such ring; LDZ must be cleaved and then must cyclize, which LDX cannot possibly do. (Tr. 647:5-7.) LDZ in Patrick is cleaved by aminopeptidase, and a POSA would have no reason to expect that LDX would be cleaved by aminopeptidase and, in fact, it is not, as taught by Sharman. (Tr. 648:13-649:24.) The Maidment reference teaches that the prodrug LDZ has a faster T_{max} and higher C_{max} than diazepam, which would be just the opposite of what is desired. (Tr. 650:10-15.) You cannot

extrapolate from one prodrug to another, and the prodrug behavior in the body varies with the route of administration. (Tr. 650:16-23.) Neither Miller nor Patrick addresses reducing drug abuse. (Tr. 651:11-15.) Dr. Mallamo is correct that there are some significant similarities between the structures of d-amphetamine and metaraminol, but there are also significant differences; in any case, it is well-known that structurally similar compounds can have markedly different pharmacological properties. (Tr. 652:3-11.) Claim 1 of Miller covers 1,360 different promoieties, of which only a small fraction are free amino acids rather than their acylated derivatives. (Tr. 654:11-24.) Dr. Mallamo mischaracterized the scope of claim 1 and ignores the fact that the amino acids there include both standard and nonstandard amino acids. (Tr. 655:3-9.) Dr. Klibanov sees no reason why, based on the Bhagavan reference, it would be obvious to try l-lysine. (Tr. 655:10-14.) As to Miller's formula II, there are many hundreds of preferred acyl groups, and only a small subset of compounds are free amino acids. (Tr. 655:19-23.) Dr. Mallamo's demonstrative did not show all of Formula II, which includes the acylated derivatives. (Tr. 656:5-12.) Miller has 32 numbered examples, most of them with acylated amino acid promoieties and none with free l-lysine. (Tr. 656:13-19.) Miller expressly states a preference for acylated promoieties. (Tr. 656:20-657:2.) I disagree with Dr. Mallamo that Example 5 contains free l-lysine; it seems to have a typo and neither says nor means l-lysine, which a POSA would understand. (Tr. 657:7-658:9.)

In a different patent case before the PTO in May of this year, Dr. Sloan asserted: "it is very difficult, unpredictable, and challenging to find a prodrug suitable to overcome a particular barrier." (Tr. 660:3-8.) He went on to state that for prodrugs that are cleaved enzymatically, due to the variability of enzymes, there is further unpredictability of any prodrug candidate. (Tr.

660:9-13.) I agree with Dr. Sloan that any prodrug candidate is unpredictable, and you cannot mechanically extrapolate from one prodrug to another. (Tr. 660:14-17.) I agree with Dr. Sloan that potential instability of prodrugs is one reason they are unpredictable, and I have had significant experience with prodrugs. (Tr. 662:3-6.) Dr. Mallamo published a paper in which he tried to make a prodrug with l-lysine as the promoiety, and he found that it was not stable, so he had to change it to a polypeptide promoiety. (Tr. 662:7-18.) Dr. Mallamo cited two papers by Pochopin, but not a third from 1995, in which the authors tried to form a prodrug of the drug Prazosin using lysine as the promoiety. (Tr. 663:4-11.) They found that the l-lysine prodrug of Prazosin was unstable and rapidly degraded. (Tr. 663:11-16.) Dr. Mallamo indicated that modifying amphetamine's free amino group will inactivate it, but that is untrue: if you modify that amino group with a methyl group, you get methamphetamine, which is a drug and not inactive. (Tr. 665:17-666:1.) Dr. Mallamo's lead compound analysis is based on hindsight. (Tr. 666:13-17.) Dr. Mallamo's reference, AACAP 1997, recommends nonstimulants for reducing abuse, which Dr. Mallamo dismissed. (Tr. 666:23-667:5.) Dr. Mallamo also dismissed using l-amphetamine or a mixture of the two, although the Epstein reference teaches that the l-isomer has not been shown to be addictive. (Tr. 667:10-16.) The AACAP 1997 reference also states that methylphenidate has lower abuse potential than d-amphetamine and abuse of methylphenidate is rare. (Tr. 668:4-13.) There were other approaches to attempt to reduce abuse, other than modifying the d-amphetamine molecule, such as forming noncovalent complexes of d-amphetamine, using cyclodextrin as one example. (Tr. 669:2-8.) One can develop formulations that cannot be easily abused; I am an inventor on nine U.S. patents for formulations of d-amphetamine that cannot be easily abused; formulations with the consistency

of a gummy bear cannot be simply crushed. (Tr. 669:9-23.) There were many alternative promoieties to lysine, many much simpler ones, such as acetyl groups. (Tr. 670:2-10.) Dr. Mallamo cited Rips 1981, a patent, which discloses prodrugs with a promoiety that is at least a dipeptide or longer, not a mono amino acid. (Tr. 671:1-7.) The Pochopin 1994 reference cited by Dr. Mallamo taught that the elimination of the d-amino acyl prodrug of the drug DDS was much slower than for the l-isomer, which would be desirable for a prodrug, and states that d-amino acyl derivatives may be useful for sustained release forms. (Tr. 671:20-672:5.) Biel 1972 and 1975 illustrate the use of d-lysine, rather than l-lysine. (Tr. 672:8-12.) Piccariello 2002, cited by Dr. Mallamo, describes a prodrug with a polypeptide as the promoiety, not a single amino acid, and also mentions both the l- and d-isomers of amino acids. (Tr. 672:21-673:7.) A POSA would not have been motivated to combine the PDR with either Patrick or Miller to arrive at LDX with a reasonable expectation of success. (Tr. 673:22-674:6.) Dr. Mallamo thought isolated LDX was obvious, but neglected to explain how a POSA would have isolated it. (Tr. 674:10-18.)

Kibbe's Handbook of Pharmaceutical Excipients describes hundreds of excipients, and Dr. Mallamo did not explain why he chose the ones he did. (Tr. 675:18-676:5.) Dr. Mallamo's dosage calculations relied on the assumption that LDX is completely cleaved within the body, and, in 2003, there was no evidence of that. (Tr. 676:10-23.)

On cross-examination, Dr. Klibanov said that the reference showing that LDZ had a faster T_{max} and higher C_{max} than diazepam involved intramuscular injection, not oral administration. (Tr. 683:5-17.) He agreed that, in 2003, a POSA would have understood that control or regulation of the release of amphetamine in vivo could minimize the spike in drug

levels, and a POSA might have been motivated to achieve that. (Tr. 687:14-22.) Dr. Klibanov agreed that he said that at his deposition, but it was prefaced by the condition, if a POSA somehow miraculously chose dextroamphetamine as a lead candidate. (Tr. 689:3-22.) If a POSA selected d-amphetamine, the POSA would have been motivated to markedly regulate its release in vivo to minimize the spike in drug levels. (Tr. 690:20-25.)

O. Testimony of Nisha Marie Mody

Dr. Mody was admitted as an expert in economics and commercial success. (Tr. 694:13-15, 696:25-697:3.) She stated that she concluded that Vyvanse® has been commercially successful since its launch and that features unrelated to the patented features do not explain that success. (Tr. 695:3-7.) The sales records show that Ms. Whitehouse's characterization of Vyvanse® as a blockbuster product is correct. (Tr. 699:19-24.)

P. Testimony of Leonard Chyall

Dr. Chyall was admitted as an expert in organic and pharmaceutical chemistry, and pharmaceutical salt screening, selection, and analytical testing. (Tr. 710:19-24.) Dr. Chyall said that he disagreed with Dr. Sloan that salts of LDX would have been obvious to a POSA. (Tr. 715:2-5.) A POSA can predict whether a salt would form from an acid-base reaction; the procedures for forming pharmaceutically acceptable salts are well-known in the art. (Tr. 717:9-21.) I disagree with Dr. Sloan that a POSA would believe that it is usually better to formulate with a salt form, because, even though salt forms are prevalent in the pharmaceutical industry, it is not generally true that they are the appropriate approach for every compound. (Tr. 718:3-10.) Marketed pharmaceutical products may be in non-salt forms such as the neutral molecule, the free base, or the free acid, among many options. (Tr. 718:11-15.) Salt forms do not always

import beneficial properties. (Tr. 719:2-4.) The Bighley reference does not support Dr. Sloan's opinion that a POSA would do salt screening even in the absence of issues with the free base form of the drug, but rather supports the opposite position. (Tr. 719:17-24.) Bighley states that the first decision to be made concerns the viability of a neutral compound; a POSA would need to evaluate the neutral compound's solubility, stability with respect to melting point, hygroscopicity, the presence of multiple crystalline forms, and the ability to crystallize. (Tr. 720:4-17.) Bighley presents a flowchart of steps after evaluation of the viability of the free base. (Tr. 720:20-25.) For a basic compound, the next step, if there is a need to modify the neutral compound, is to prepare the hydrochloride salt form. (Tr. 720:23-721:3.) Bighley states that hydrochloride salts are most commonly used, at about 44%, followed by sulfate salts, at about 6%; mesylate salts (not including dimesylates) are at about 3%. (Tr. 721:25-722:16.) Dr. Sloan opined that, contrary to the teachings of Bighley, the POSA would have passed over the hydrochloride salt in favor of other salts like the mesylate. (Tr. 723:1-3.) While it is true that hydrochloride salts can have problems, Bighley teaches that, nonetheless, you examine them first to see if those problems arise. (Tr. 723:4-15.) This area of chemistry is highly unpredictable; the properties of solids must be determined by experimentation. (Tr. 723:16-20.) Gould also says that you should start with the hydrochloride salt. (Tr. 724:1-7.) The inventors began with the hydrochloride salt of LDX and, as Dr. Verbicky testified, it was a hygroscopic foam. (Tr. 724:8-16.) The Serajuddin reference was published in 2007. (Tr. 725:2-3.) If the POSA finds that the HCL salt does not work, it makes sense to start a salt screen. (Tr. 725:21-25.) Gould, Stahl, and Berge all teach a POSA which acids to include in a salt screen. (Tr. 726:10-16.) The prior art taught away from mesylate salts, because the processes used to

prepare them form toxic impurites. (Tr. 727:6-15.) Stahl warns that mesylate salts can become contaminated by mesylate esters, which are poisonous. (Tr. 727:16-24.) After salt screening, the POSA assembles a shorter list of salts for more detailed evaluation. (Tr. 728:13-22.) The Davies reference states: "there is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity." (Tr. 729:7-22.) The Bastin reference discusses salt selection for three different candidate drugs, concluding that one was best as the neutral molecule, one was best as a sulfate salt, and one was best as a mesylate salt in a crystalline monohydrate form. (Tr. 730:18-731:6.) The Engel reference does not relate to amphetamines. (Tr. 732:6-19.) A POSA cannot predict properties of a salt based on a structurally similar compound, as the Davies reference shows. (Tr. 732:20-733:7.) LDX is a diamine, with two amine functional groups, while d-amphetamine has only one. (Tr. 737:1-10.) The Ahlneck reference speaks generally to the effect of water on compounds. (Tr. 739:2-5.) Ahlneck would not have motivated a POSA to reduce the water content of LDX, as Ahlneck focuses on crystalline properties that would not be known prior to studies of LDX dimesylate. (Tr. 739:9-25.) I agree with Dr. Sloan that a POSA would expect that a nonhydrated form of LDX dimesylate would be below 3.8% water, but this does not apply to possible hydrated phases of LDX dimesylate, in which water has a beneficial effect that improves stability; reducing such water content destroys crystalline stability. (Tr. 740:1-13.) AMRI did a study for Shire of water content in LDX dimesylate, and found stability problems in the presence of atmospheric moisture above 65% relative humidity; drying that product resulted in 15% water content. (Tr. 740:14-741:19.) It is surprising that the inventors were able to discover a stable formulation that addresses this hygroscopicity issue with LDX dimesylate. (Tr. 741:20-742:2.) The patents

with dimesylate salt claims all have disclosures of a procedure to make the dimesylate, essentially a recipe. (Tr. 743:23-744:22.) This is Figure 2 and Example 2 in the '630, '031, '770, and '030 patents. (Tr. 745:3-6.) As to the patents with claims reciting pharmaceutically acceptable salts, the '770 and '561 patents, the patents contain the example of the dimesylate salt, and the POSA could modify it so that, instead of isolating the compound in the acid form to get the free base form, one could make other pharmaceutically acceptable salts. (Tr. 745:16-746:3.) The '770 patent also discusses exemplary pharmaceutically acceptable salts. (Tr. 746:4-14.) The Berge and Gould references also discuss pharmaceutical salts. (Tr. 746:12-22.) As to claim 12 of the '735 patent, which recites a pharmaceutically acceptable salt of LDX, there is a working example of formation of the dihydrochloride salt of LDX, which a POSA could modify to make other salts. (Tr. 747:3-17.) As to claim 4 of the '486 patent, there is the same working example of the dihydrochloride salt, which a POSA could modify to make the monomesylate salt. (Tr. 748:9-18.) All the patents with salt claims claim priority to the '619 and '526 applications, which disclose the working example of making the dihydrochloride salt, which a POSA could modify to make other salts. (Tr. 748:19-749:23.) By reading the patent specifications and consulting the Stahl and Berge references, a POSA would know which acids can be used to make pharmaceutically acceptable salts of LDX. (Tr. 750:11-17.) A first stage development report for a study conducted for Norwich shows that the Stahl reference was consulted to build their list of pharmaceutically acceptable acids. (Tr. 751:9-24.) It is surprising and unexpected that Vyvanse® has an amide linkage so stable that it cannot be cleaved chemically to release abusable d-amphetamine, as discussed in the '630 patent. (Tr. 752:3-753:5.) It is also surprising that a study conducted for New River shows that the

compound cannot be cleaved in a lab using enzymatic processes; 15 different enzymes were tried. (Tr. 753:7-754:7.)

On cross-examination, Dr. Chyall stated that, as to claim 10 of the '770 patent, a pharmaceutically acceptable salt is one with a nontoxic counterion and sufficient stability that a salt would form, not with all the desirable properties for commercialization. (Tr. 756:11-757:8.) The POSA could predict whether the acids listed in Stahl would form salts with a target compound, but could not predict the physical properties of the resulting solid. (Tr. 759:12-22.) A POSA could predict whether the reaction with the acid would provide the salt and whether that salt had a high yield. (Tr. 759:24-760:21.) When AMRI prepared a dihydrochloride salt of LDX and got a hygroscopic foam, it was a pharmaceutically acceptable salt within the meaning of claim 10 of the '770 patent. (Tr. 762:3-763:5.) Dr. Chyall said that he had never designed a prodrug. (Tr. 765:18-20.)

Q. Testimony of David Taft

Dr. Taft was admitted as an expert in pharmacokinetics and pharmacodynamics. (Tr. 769:11-21.) As to claims 6 and 9 of the '561 patent, claims 4 and 25 of the '030 patent, claim 10 of the '770 patent, and claim 12 of the '735 patent, the PK and therapeutic limitations are not inherent to LDX, nor would the PK and therapeutic effects of LDX have been predictable. (Tr. 770:12-22.) The PK characteristics of a drug in formulation depend on more than the drug alone; there are numerous factors, including preparation and manufacture, its physical chemical properties, the particular salt form, the excipients and their amounts, and the kind of dosage form. (Tr. 771:18-772:10.) Norwich's witness, Dr. Fackler, testified that each of these factors could influence PK. (Tr. 773:5-9.) The title of the Davies reference is "Changing the Salt,

Changing the Drug," and it teaches that changing the salt can change the properties of the molecule. (Tr. 774:2-10.) It can vary the solubility and the rate of dissolution, which can affect bioavailability and PK profile. (Tr. 774:11-16.) A page in a New River lab notebook shows this clearly; the different PK profiles of different LDX salts show that PK characteristics of LDX are not inherent. (Tr. 774:19-775:16.) It is well-known that the choice of excipients and their proportions in a formulation can affect the PK profile, whether immediate or modified release. (Tr. 775:19-24.) When formulators change the release rate, C_{max}, T_{max} and AUC change. (Tr. 776:3-10.) Norwich's product development report discusses the potential impact of choice of excipient on drug release. (Tr. 776:21-777:19.) It says that over-lubrication can reduce drug release, and the risk that magnesium stearate will affect drug release is medium. (Tr. 777:20-778:4.) It is well-known that use of an enteric coating will delay release; the concentration time profile and T_{max} are different. (Tr. 778:12-779:8.) One could formulate LDX so as to delay the release and obtain a T_{max} that does not fall within the claim limitations. (Tr. 779:16-25.) The Ermer 2012 study showed the change in PK characteristics. (Tr. 780:2-15.) The patent in JTX-15 (the '561 patent), column 13 lines 42 to 45, describes an embodiment in which use of a hydrophilic polymer enhances or achieves a sustained release profile. (Tr. 786:5-16.) The PK characteristics of LDX dimesylate were not predictable in the absence of testing. (Tr. 788:3-13.) One could not predict whether the prodrug would convert in the body after administration, where it would convert, the rate and extent of conversion, the effect of the salt form (as Dr. Moghaddam testified), or the absorption characteristics. (Tr. 788:9-789:6.) A POSA could not predict the effect that the choice of promoiety would have on PK characteristics of the prodrug. (Tr. 789:11-15.) Table 61 in the '561 patent shows how the use of different

promoieties changes the PK characteristics of the prodrug; absent testing, one cannot predict that. (Tr. 789:7-790:2.) The Heal poster shows a surprising and unexpected hysteresis effect with d-amphetamine relative to LDX. (Tr. 790:25-791:9.) The counterclockwise hysteresis – the activity of the drug is maintained even after the concentration starts to climb – is unexpected. (Tr. 793:4-15.) Heal stated that LDX is likely to have an enlarged therapeutic window compared to immediate release d-amphetamine; LDX shows unusual PK properties. (Tr. 793:25-794:8.)

On cross-examination, Dr. Taft stated that he has not treated patients with ADHD, has never designed a prodrug, and is not a formulator. (Tr. 796:24-797:7.)

R. Deposition Testimony of David Baker

Mr. Baker stated that he is vice president of commercial strategy and new business at Shire. (Tr. 808:19-25.) He was designated as a 30(b)(6) witness for Shire. (Tr. 809:10-16.) He had previously been product general manager for Vyvanse®. (Tr. 810:5-11.) Shire's strategy was to convert physician prescribing from Adderall XR to Vyvanse®. (Tr. 813:4-19.) At the time of the launch of Vyvanse®, sales reps stopped promoting Adderall XR. (Tr. 815:20-816:1.) Shire primarily wanted to convert physicians to prescribing Vyvanse® because it is a better product. (Tr. 816:20-22.) It was longer acting and had less abuse-related liking effects, and had less variation in the PK effects. (Tr. 817:2-12.) Vyvanse® also showed less end-of-day irritability. (Tr. 817:23-24.) We received lots of feedback from physicians that Vyvanse® exceeded expectations. (Tr. 818:14-20.) The effect size we saw with Vyvanse® was higher than any we had seen with Adderall XR, which was surprising. (Tr. 820:9-21.)

S. Rebuttal Testimony of John Mallamo

Dr. Mallamo said that the chemical stability, as well as other properties, of the amide bond between d-amphetamine and l-lysine would have been well-known to a POSA. (Tr. 823:19-22.) Both Pochopin and Bundgaard state that good chemical stability and potentially rapid enzymatic hydrolysis in vitro suggest that these compounds would make good prodrugs. (Tr. 824:8-13.) Both say that certain amides formed with amino acids may be susceptible to enzymatic cleavage in vivo. (Tr. 824:16-18.) Pochopin 1995 describes several dapsone amino acid conjugates, and found that the lysine conjugate had its maximum stability in the range of physiological pH. (Tr. 825:7-10.) The l-lysine conjugate also was shown to break down rapidly in enzymatic assays. (Tr. 825:12-17.) This teaches the POSA that it is a stable bond that survives ingestion, transits to the luminal area, and there is absorbed rapidly. (Tr. 825:17-24.) A POSA would have expected that l-lysine could be used with other drugs and have chemical stability. (Tr. 826:3-6.) The Shashoua '137 patent teaches that the covalent bond between the drug and the promoiety is an amide bond, which is inherently stable and would allow for transit in the GI to the place where it is absorbed. (Tr. 827:17-23.) Piccariello says the same thing. (Tr. 827:24-828:2.) Charette 1998 teaches the strength of amide bonds and their strength against cleavage. (Tr. 828:7-24.)

On cross-examination, Dr. Mallamo said that d-amphetamine is not the closest prior art to LDX, but agreed that he did write that in his report. (Tr. 829:12-830:8.)

T. Rebuttal Testimony of Neil S. Kaye

Dr. Kaye stated that Dr. McGough's views about the reduced abuse potential of Vyvanse® are exaggerated. (Tr. 831:22-25.) The black box warnings on the Vyvanse® label

should cause a physician to avoid prescribing Vyvanse® to patients prone to substance abuse. (Tr. 833:1-22.) The label refers to two studies which show that the abuse potential is similar to other amphetamine drugs and is dose-related. (Tr. 834:1-12.) The studies showed that a higher dose of Vyvanse® produces the same drug-liking effects as 40mg of d-amphetamine. (Tr. 834:13-17.) From my experience as a physician, Vyvanse® can be abused by taking a higher dose or buying an OTC enzyme product which converts the prodrug into d-amphetamine. (Tr. 834:18-835:4.) The duration of action of Vyvanse® is not clinically significant; there were other extended release drugs. (Tr. 835:17-836:1.) My patients taking Vyvanse® have not experienced a longer duration of action than other drugs; individual variations are the same or longer than a one or two-hour difference. (Tr. 836:2-12.) The McCracken study of Adderall XR showed a 12-hour duration of action. (Tr. 836:14-838:3.) My experience agrees with the conclusion of the Cochrane review: these drugs all work. (Tr. 839:2-13.) I have no preference for prescribing one drug over another. (Tr. 839:14-23.) Vyvanse® can negatively impact sleep; the package insert itself says this. (Tr. 840:22-841:4.) The low PK variability of Vyvanse® is not clinically relevant and did not meet a long-felt need. (Tr. 842:6-21.) I do not see the larger effect size found in research in my clinical experience with patients; all of these drugs work. (Tr. 844:1-19.) Dr. Kaye stated that he is not aware of any industry praise for Vyvanse®. (Tr. 845:15-21.) The 2011 medical letter recommends use of an oral stimulant but expresses no preference for which one. (Tr. 846:15-847:7.)

On cross-examination, Dr. Kaye said that a POSA would have understood that LDX had a reduced potential for abuse and would have been motivated to prescribe it in a patient prone to abuse it. (Tr. 850:25-851:10.) While the duration of action stated on the product labels of

Vyvanse® and Adderall XR is different, I see no clinically meaningful difference. (Tr. 851:15-852:13.)

DISCUSSION

The parties raised no material disputes about the characteristics of the person of ordinary skill in the art ("POSA"); both parties contend that the opinions of their expert witnesses would not change if the definition of the POSA was that offered by the other side. (PFOF ⁋ 120; DFOF ⁋ 35.)

I. Patent invalidity due to obviousness

Norwich contends that all asserted claims are invalid as obvious.

The parties have agreed to the following Priority Dates: claim 12 of the '735 patent – May 29, 2003; claim 1 of the '630 patent, claims 4 and 25 of the '030 patent, claim 4 of the '486 patent, claim 7 of the '031 patent, and claim 5 of the '770 patent – June 1st, 2004; and claim 4 of the '630 patent, claim 14 of the '466 patent, and claims 1, 6 and 9 of the '561 patent – January 6th, 2006. (DDX-314.) The parties dispute the Priority Date of claim 10 of the '770 patent.

The patents in this case all concern a new chemical compound, l-lysine-d-amphetamine ("LDX."). The Federal Circuit applies the "lead compound analysis" to questions of the obviousness of new chemical compounds; both these points are undisputed. The principles of the lead compound analysis are set forth in the Federal Circuit's decision in Eisai, an early post-KSR decision which interprets and summarizes KSR:

> The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve

> the claimed compound. *See Takeda*, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc*., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd, 533 F.3d 1353, 1359 (Fed. Cir. 2008). In this quote from Eisai, the Federal Circuit explains that, post-KSR, the starting reference point is the point in time at which a POSA identified a problem.

> Under Federal Circuit law, the lead compound analysis has two steps:
>
> Our case law demonstrates that whether a new chemical compound would have been prima facie obvious over particular prior art compounds ordinarily follows a two-part inquiry. First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts.
> . . .
> The second inquiry in the analysis is whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success.

Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1291-92 (Fed. Cir. 2012).

A. Identifying the problem to be solved

In the instant case, the parties do not dispute that d-amphetamine was a known, effective treatment for ADHD and that the abusability of d-amphetamine was a known problem, as

reflected in the PDR black box warning.[1] The POSA would have identified the abusability problem of d-amphetamine as the problem to be solved, the starting point for the obviousness inquiry.

While this definition of the problem to be solved – the abusability of d-amphetamine – is undisputed and seems straightforward, Norwich never defines a key term: abuse. Defendant's post-trial brief leaves vague what "abuse" of prescription amphetamine medication encompasses. This makes it difficult to carefully evaluate Defendant's arguments about the POSA's obvious solution to a vaguely stated problem. The closest that Norwich comes to a definition is implied in proposed Findings of Fact ¶ 321: "A POSA would have known that dextroamphetamine drugs were commonly abused by mechanical manipulation of the tablets, including by crushing the tablets and then snorting or injecting the resulting powder." This is supported by the testimony of Takeda's expert, Dr. McGough, who discussed the nature of the abuse problem with d-amphetamine. Dr. McGough has decades of experience in the development of medications for the treatment of ADHD, and a very impressive resume; he stood out as an expert in that particular field. (Tr. 463:2-9.) Dr. McGough testified:

> Q. Let's go to the first one which is reduce abuse potential. Okay, what is meant by abuse potential?
>
> A. So as I said there were two big problems that were, you know, even described by the DEA in the source Norwich presented yesterday, there was a problem with illicit diversion, the medications getting to the hands of people to whom it wasn't intended. The other extended release formulation solved that need to some extent, but the second unmet need was really the ability to abuse the compound, to manipulate them, extract the active stimulate, crush it, liquefy it, snort it, inject it, which again would basically give you a compound like cocaine.

[1] The warning in the PDR listing for Dexedrine® brand of d-amphetamine sulfate states: "AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE." (DTX-054 at 3083.)

(Tr. 491:4-15.) Dr. McGough explained that the two big problems with the abuse of amphetamines were: 1) illicit diversion, which extended release formulations solved to some extent; and 2) abuse through crushing the amphetamine tablet and snorting or injection. No one in this case has focused on the problem of illicit diversion, which Dr. McGough said had been solved to some extent. Rather, the parties and the witnesses consistently referenced the problems of crushing, snorting, and injection. The Court thus defines the problem of d-amphetamine abuse as the problem arising from the crushing of tablets, following by snorting or injection. Despite the fact that Norwich never expressly defined the problem of the "abuse" of d-amphetamine medications, the Court is satisfied that this is the intended meaning.

B. Selecting the lead compound

Next, the Court inquires as to whether the POSA would have selected a particular prior art compound as a starting point for further development efforts:

> While the lead compound analysis must, in keeping with KSR, not rigidly focus on the selection of a single, best lead compound, the analysis still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art.

Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (citation omitted).

Norwich contends that a POSA would have selected d-amphetamine as the lead compound: "d-amphetamine was a promising compound for modification." (Def.'s Br. at 4.) In support, Norwich points to the undisputed fact that d-amphetamine was an established and effective treatment for ADHD, as stated in the PDR. Norwich points as well to Dr. Klibanov's agreement that d-amphetamine was a promising compound for modification. (Tr. 668:16-19.)

Norwich offers a list of reasons why a POSA would have selected d-amphetamine over a number of other compounds used for treatment of ADHD. (Def.'s Br. at 5-6.)

Takeda appears to disagree, titling a subsection, "A POSA Would Not Have Selected D-Amphetamine as a Lead Compound for Further Development to Reduce Abuse." Yet the part of the brief that follows does not offer a persuasive argument that d-amphetamine would not have been selected. Instead, Takeda criticizes aspects of Defendant's presentation on various grounds, arguing that Dr. Mallamo's testimony on the selection of the lead compound should be given little weight, for various reasons. Takeda also contends: "Dr. Mallamo's selection of a lead compound completely failed to consider his stated goal of reducing abuse in selecting the lead compound." (Pls.' Br. at 13.)

Takeda has not effectively challenged Norwich on the matter of the selection of d-amphetamine as lead compound. Neither party notes this, but, in this case, the choice of lead compound follows directly from the definition of the problem and was indeed "a natural choice for further development efforts." Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009). Because the parties do not dispute the fundamental premise that a problem to be solved was the abusability of d-amphetamine, it does make d-amphetamine the natural choice for lead compound – and there is no evidence of record to the contrary. No one has pointed to evidence that, for the problem of the abusability of d-amphetamine, there was a better compound to start with than d-amphetamine. Takeda's challenges to Dr. Mallamo's testimony on the subject do not persuade the Court that Norwich is wrong and d-amphetamine is not the compound to start with. A POSA would have selected d-amphetamine as the lead compound.

C. The motivation to modify the lead compound

The Court next determines "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." Otsuka, 678 F.3d at 1292. Norwich sensibly divides the process of modifying d-amphetamine into two principal steps: 1) a POSA looking to reduce the abuse potential of d-amphetamine would have been motivated to modify d-amphetamine by conjugating it into a prodrug ("the Prodrug Step"); and 2) a POSA looking to reduce the abuse potential of d-amphetamine by making a prodrug would have been motivated to select l-lysine as the promoiety ("the Promoiety Step.")

1. The Prodrug Step

Norwich begins the discussion of modifying d-amphetamine with some fundamental propositions about the POSA's knowledge about d-amphetamine, abuse, euphoria, and related topics:

> Takeda also conceded that a POSA knew that euphoria is the side-effect of d-amphetamine that can lead to cravings and abuse. NFOF ¶¶ 265-68. Still further, Takeda conceded that euphoria is caused by the rapid onset, or initial spike, in levels of d-amphetamine in the blood. NFOF ¶¶ 321-22. Accordingly, Takeda's expert Dr. Klibanov admitted that "the POSA would have been motivated to markedly regulate the release of dextroamphetamine in vivo . . . in order to minimize the spike in drug levels." NFOF ¶ 324. Thus, a POSA had reason to modify d-amphetamine to minimize the euphoria side-effect that contributed to its abuse potential. NFOF ¶¶ 263, 271, 273-74, 280-84, 323-24.
> . . .
> As just discussed, there is no dispute that the POSA would have known that euphoria is associated with the rapid initial spike in drug levels. It is also undisputed that Patrick discloses a prodrug designed precisely to avoid a side effect (drowsiness) caused by the rapid spike of the drug (diazepam). NFOF ¶¶ 80-83, 281-82, 386, 408-09, 481. Dr. Mallamo explained that the prodrug disclosed in Patrick accomplishes this by "creating essentially a sustained release effect," thereby "reducing the initial plasma levels." NFOF ¶ 409. Miller similarly discloses using a prodrug strategy to prolong the release of metaraminol, an anti-

> hypertensive drug, to diminish side-effects associated with the rapid onset of the drug. NFOF ¶¶ 104-07, 115-18, 283-84, 387, 410-12, 513-514, 526-28. Thus, a POSA had ample reason to use a prodrug approach as taught in Patrick and Miller to reduce the abuse potential of d-amphetamine. E.g., NFOF ¶¶ 281-85, 481, 514.

(Def.'s Br. at 7-8.)

To allow for an organized examination of Defendant's arguments about the Prodrug Step, the Court has distilled Defendant's arguments into component propositions and resulting conclusion:

> A POSA would have believed:
>
> 1. Euphoria is an effect of administration of d-amphetamine
>
> 2. Euphoria results from initial spiking in the plasma concentration curve of d-amphetamine
>
> 3. The euphoric effect of d-amphetamine can lead to its abuse
>
> 4. A prodrug can change the plasma concentration curve to reduce initial spiking
>
> 5. Decreased initial spiking results in decreased euphoria which results in decreased abuse
>
> Therefore: a prodrug which decreases initial spiking will result in decreased abuse.

The Court will examine each proposition in order.

Proposition 1 is taught by the PDR and is undisputed.

In support of Proposition 2, Norwich cites Defendant's proposed Findings of Fact ("DFOF") ⁋⁋ 321 and 322, which in turn cite Dr. Klibanov's testimony:

> Q. And one of the ways that they were abused was by mechanical manipulation of the tablets, correct?
>
> A. That's my understanding.

Q. So in other words, the tablets could be crushed by users. Is that right?

A. That's my understanding.

Q. And abusers would snort or inject them, correct?

A. Correct.

Q. And it was that crushing that would then lead to a spike of dextroamphetamine in the blood, correct?

A. That is my understanding.

Q. And that caused the euphoria, correct?

A. Again, that's what I understand.

Q. And generally speaking, a POSA at the time would have understood that if you were able to control or regulate the release in vivo of dextroamphetamine, you would be able to minimize the spike in the drug levels, correct?

A. Yes.

Q. And you agree that a POSA would have been motivated to markedly regulate the release of dextroamphetamine in vivo in order to minimize the spike in drug levels, correct?

A. Not necessarily but it certainly is a possibility.

(Tr. 687:4-25.) In this testimony, the subject is the snorting or injection of crushed tablets of d-amphetamine.[2] Dr. Klibanov testified that, when tablets are crushed and injected or snorted, a spike in blood levels caused euphoria, and that a POSA would know that controlling the drug release could minimize the spiking. This supports Proposition 2, but with the limitation that the euphoria results from spiking after crushing of the tablets and administration of crushed tablets

[2] The Court notes that Norwich cited this testimony in support of its contention about what a POSA would have known about the abuse of d-amphetamine, and Dr. Klibanov's testimony is consistent with the Court's understanding that the problem of prescription d-amphetamine abuse is limited to the crushing of tablets, snorting, and injection.

through snorting or injection.

> In support of Proposition 3, Norwich cites the Masand reference:
>
> All agents labeled as psychostimulants, central nervous stimulants, or amphetamine-based appetite suppressants have abuse potential. Their capacity to produce euphoria and a sense of well-being can lead to craving and compulsive use.

(DTX-363 at 540.) Norwich also cites Dr. Mallamo's testimony about Masand:

> Masand talks to us about that all these agents that are labeled psychostimulants or central nervous stimulants or amphetamine-based appetite suppressants have abuse potential. Their capacity to produce euphoria and the sense of wellbeing can lead to craving, addiction, compulsive disorders.

(Tr. 92:16-21.) Dr. Mallamo expands Masand's teaching from craving and compulsive use to craving, addiction, and compulsive disorders. Norwich also cites Dr. Mallamo's testimony that "from the PDR we see that the euphoric side effect is what drives the abuse," but this Court does not find that the PDR supports Dr. Mallamo's assertion: other than listing euphoria as one of twelve CNS adverse reactions, the PDR entry for Dexedrine® contains no other information about euphoria, nor does it relate euphoria in any way to amphetamine abuse. (Tr. 92:13-14; DTX-54 at 3084.) Norwich also points to Dr. Klibanov's agreement with the proposition that "a POSA would have understood that euphoria can lead to cravings and compulsive use." (Tr. 686:23-25.) Contrary to Defendant's characterization, Dr. Klibanov did not agree that "a POSA knew that euphoria is *the* side-effect of d-amphetamine that can lead to cravings and abuse." (Def.'s Br. at 7; italics added.) Dr. Klibanov agreed that a POSA would know that euphoria was *a* potential side effect of d-amphetamine, and that a POSA would understand that "euphoria can lead to" cravings and compulsive use. The evidence of record supports Proposition 3: the

euphoric effect of d-amphetamine can lead to[3] its abuse through crushing, snorting, and injection.

As to Proposition 4, Norwich cites the Patrick reference. In one section, titled, "Prodrugs to prolong drug activity," Patrick teaches the use of prodrugs to produce "more sustained action" of the drug. (DTX-449 at 243.) In the next section, titled, "Prodrugs masking drug activity and side effects," Patrick states: "Prodrugs can be used to give a slow release of drugs . . ." (DTX-449 at 245.) This section also gives the example of the prodrug LDZ, "a diazepam prodrug which avoids the drowsiness side-effects associated with diazepam. These side effects are associated with the high initial plasma levels on administration, and the use of a prodrug avoids this problem." (DTX-449 at 246.) Norwich also cites Miller, which teaches use of a prodrug to address a problem of rapid release of the active, with the effect of moderating and regulating that release. See, generally, '796 patent, col.1. Defendant's brief cites to proposed Findings of Fact statements which cite the Bundgaard reference, which begins with a paragraph setting out the general principles of the use of prodrugs to modify the release profile of a drug, producing either rapid or sustained release.[4] (DTX-113-1.) The evidence supports Proposition 4: a prodrug can change the plasma concentration curve to reduce initial spiking.

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[3] The Masand reference, and both Drs. Mallamo and Klibanov, used or agreed to the same wording to express the relationship between euphoria and abuse: euphoria "*can lead to*" more serious abuse of d-amphetamine. (DTX-363 at 540; Tr. 686:23-25; 92:16-21.)

[4] Bundgaard provides a helpful introduction to prodrugs. (DTX-113-1.) Bundgaard explains that – contrary to what Norwich frequently seemed to imply – the designer of the prodrug can design it to produce a rapid rate of conversion to the active drug, or to produce a slow rate of conversion to the active drug. Bundgaard further explains: "The necessary conversion or activation of prodrugs to the parent drug molecules in the body can take place by a variety of reactions. The most common prodrugs are those requiring a hydrolytic cleavage mediated by enzymic catalysis." (Id.)

The Court has reviewed the first four factual propositions that form the basis for Defendant's contentions about the Prodrug Step. As Norwich contends, the use of prodrugs to modify drug release characteristics and the plasma concentration curve, including initial spiking in the curve, was well known in the prior art. The euphoric effect of d-amphetamine, its basis in initial spiking in the plasma concentration curve, and that euphoria can lead to abuse of d-amphetamine when crushed and snorted or injected, were all known. While Plaintiffs challenge Dr. Mallamo's testimony on various grounds, Plaintiffs do not contest these teachings of the relevant prior art references, and do not substantially contest the factual support for these propositions. That changes, however, as to Proposition 5 and the conclusion.

Proposition 5 and the conclusion combine the preceding propositions to build a theory: decreased initial spiking of d-amphetamine release results in decreased euphoria which results in decreased abuse through crushing, snorting, and injection; therefore, a POSA would have had the motivation to combine a prodrug with the d-amphetamine abuse problem to solve it. Norwich expresses this in its discussion of two related propositions (the "Norwich Propositions"): 1) "a POSA had reason to modify d-amphetamine to minimize the euphoria side-effect that contributed to its abuse potential" (Def.'s Br. at 7); and 2) "a POSA had ample reason to use a prodrug approach as taught in Patrick and Miller to reduce the abuse potential of d-amphetamine." (Id. at 7-8.)

The first Norwich Proposition appears largely, but not entirely, supported: the evidence reviewed so far does show that a POSA would have been motivated to minimize the euphoria side-effect that contributed to d-amphetamine's abuse potential. To this point, Norwich has not presented evidence from the prior art that suggests that some chemical modification of d-

amphetamine itself would minimize the euphoria. But the evidence certainly supports the proposition that the POSA would have been motivated to do something to minimize the euphoric effect to reduce d-amphetamine's abuse potential. The key question is, what solutions did the prior art suggest? Norwich does not, however, assess the possible alternative solutions offered by the prior art, a point that Dr. Klibanov made at length and which Norwich acknowledges. (Def.'s Br. at 8.)

Defendant's second proposition, however, is not supported by the evidence, and appears true only if the contrary evidence is ignored; it is here that it becomes clear that Norwich has failed to prove that a POSA would have had a motivation to combine a prodrug with the d-amphetamine abuse problem to solve it. The evidence shows that prodrugs were well known in the art, and, as the Patrick reference shows, prodrugs had the potential to modify the release characteristics of a target drug, including eliminating initial spiking in the plasma concentration curve. While creation of a prodrug was one possible option among others for eliminating initial spiking, there is no suggestion in the prior art that a prodrug would have solved the d-amphetamine abuse problem. Norwich has not proven that the prior art provided a motivation to combine a prodrug with the d-amphetamine abuse problem, nor any basis to expect success from that combination.

Two reasons support this conclusion. First, Norwich failed to present evidence to support the full conclusion – the full bridge from the d-amphetamine abuse problem to the prodrug solutions. It has a few pieces, but they do not form the full bridge or motivation to combine.[5] Second, the evidence of record does not support the full conclusion but, instead,

[5] Norwich unwittingly made a graphic representation of the missing piece of the bridge in Dr.

provides much contrary evidence. There are two problems of contrary evidence here.

The first problem of contrary evidence can be stated simply: a POSA would have known that the effect of a prodrug on the plasma concentration curve is unpredictable. The evidence establishes this, and this factual determination alone defeats Defendant's theory that LDX is obvious. Dr. Mallamo admitted that a prodrug might have a faster T_{max} and higher C_{max} than d-amphetamine.[6] (Tr. 172:12-14.) Similarly, Dr. McGough explained:

> Q. So absent data such as that which you have just explained, which appears in the patent, would an amphetamine prodrug be predictable?

Mallamo's demonstrative exhibit, DDX-226, which the witness discussed at trial. DDX-226 highlights certain teachings in the 2003 Piccariello and Kirk reference (DTX-305). Dr. Mallamo highlighted in green the teachings about creating a prodrug for a controlled substance, the prodrug's providing delayed release which prevents spiking of the active, and that such a prodrug is less likely to be abused because of the diminished euphoria and "rush" effect. All these teachings are important elements of Defendant's theory in this case. DDX-226 also shows clearly a gap in the middle of the green-highlighted teachings – a key part of Piccariello's reasoning that Dr. Mallamo left out. Dr. Mallamo left out: "The enzymatic and/or chemical conditions necessary for the release of the controlled substance are either not present or of minimal activity when the novel pharmaceutical compound is introduced nasally, inhaled, or injected; thus, also preventing spiking when administered by these routes." (DDX-226; DTX-305 at [001].) Piccariello and Kirk used a piece of reasoning that Norwich left out of its theory, concerning enzymatic or chemical conditions not present or of minimal activity when the prodrug is administered by alternate routes of administration, which also prevents spiking. The point here is that Norwich agrees with much of the theory of Piccariello and Kirk but leaves out a key part – a part which uses knowledge of the enzymatic conditions existing on alternate routes of administration to provide a motivation to select a prodrug to solve the problem at hand. Without this key part, the prodrug seems to be just one option among others that provides delayed release, with nothing to suggest it would be a solution to the problem of d-amphetamine abuse. That leaves Norwich with a gap in its theory of the motivation to combine the prior art to achieve the patented solution to the problem at hand.

[6] Dr. Mallamo admitted that, at his deposition, he stated that a POSA reading Patrick would not know whether it took one minute or ten hours for enzymatic hydrolysis to cleave the promoiety off the LDZ prodrug. (Tr. 155:22-157:5.) The rate of conversion of the prodrug to the active drug cannot be predicted prior to testing. Dr. Klibanov noted that Maidment found that intramuscular injection of LDZ as well as diazepam in guinea pigs showed that the prodrug produced both a higher C_{max} and faster T_{max} than diazepam. (Tr. 650:10-25; PTX-1258.) This is consistent with the general consensus of the experts that PK characteristics of prodrugs are unpredictable.

> A. Not at all. As we can see, depending on which amphetamine prodrug you created, you would get very different results.

(Tr. 480:10-15.) The unpredictability of the PK characteristics of the *in vivo* functionality of a prodrug will be discussed in greater detail later in this Opinion. Because of this determination, Norwich cannot prove by clear and convincing evidence that a POSA would have had a reasonable expectation of success in using a prodrug to solve the d-amphetamine abuse problem.

The second problem of contrary evidence concerns the many factual errors in Norwich's attempt to link the prodrug solution to the d-amphetamine abuse problem. As Takeda contends, Defendant's theory of the reasoning by which a POSA would have chosen a prodrug solution to the d-amphetamine abuse problem is problematic and contains factual errors. Defendant's brief states:

> [T]he prior art taught that extended-release amphetamine formulations (which could potentially reduce the initial amphetamine spike associated with abuse) were abused through mechanical crushing of the tablets. NFOF ¶¶ 318-22, 347. By contrast, the prodrug approach could not be defeated by simple crushing. NFOF ¶¶ 348-49.

(Def.'s Br. at 8.) This is an important component of Defendant's theory, because it attempts to provide a bridge between the problem to be solved, the sustained release hypothesis,[7] and the

[7] At the heart of Defendant's obviousness theory is the contention that Miller and Patrick taught the use of a prodrug to moderate the release of the active ingredient and overcome the effects of rapid release of the active, creating a sustained release effect. (See DFOF ⁋⁋ 82, 83, 101, 115, 116, 117, 118, 282, 283, 289, 291, 292, 304, 305, 366, 374, 385, 386, 387, 412, 413, 462, 501, 514, 524, 545.) This is shown in Defendant's distillation of the theory in their proposed Findings of Fact:

> 282. Patrick would motivate a POSA to chemically modify dextroamphetamine to reduce its abuse potential (resulting from the rapid onset side effect of euphoria) because Patrick describes the prodrug approach as a way to avoid side effects caused by rapid onset high plasma concentrations.

selection of the prodrug to solve the problem. The gist of Defendant's arguments, as just quoted, is that a POSA would have believed that sustained release was still the solution, despite the failure of one or more extended release amphetamine formulations to improve the d-amphetamine abuse problem, because that failure was due to the fact that extended release formulations could be defeated by crushing, and prodrugs could not be defeated by crushing. The evidence does show that one extended release formulation, Adderall XR, was more abusable when crushed. See '735 patent, col.2 ll.16-28. Defendant's proposed Findings of Fact states: "The DEA Brochure discloses that the crushing of an extended release formulation basically defeats the extended release technology that was intended to sequester or moderate release of the drug." (DFOF ⁋ 320.) The DEA Brochure does not state this.[8] (DTX-171.) Dr. Mallamo did state that "[t]he crushing of an extended release formulation basically defeats that technology." (Tr. 97:22-25.) There is, however, no evidence (beyond Dr. Mallamo's unsupported assertions) that the prior art believed that extended release formulations were defeated by crushing.[9]

> 283. Miller would have reinforced a POSA's motivation to chemically modify dextroamphetamine to reduce its abuse potential (resulting from the rapid onset side effect of euphoria) because Miller describes the prodrug approach as a way to avoid side effects caused by "rapid release" of the active drug.

Defendant's theory is constructed around the proposition that a POSA would have been motivated to create a sustained-release formulation by using a prodrug, which would have resulted in a sustained-release formulation, which would have improved the d-amphetamine abuse problem.

[8] The DEA Brochure states that stimulant medication tablets are sometimes crushed and then snorted or injected, but says nothing about extended release technology or its defeat. (DTX-171-3.) Norwich and Dr. Mallamo are also mistaken about the teachings of Buck. (DFOF ⁋ 247.) Contrary to the assertions of both, Buck does not teach "that the extended release form of dextroamphetamine was an attempt to . . . circumvent some of the abusability of the drug." (DFOF ⁋ 247; DTX-112.) Buck does not refer to abuse or abusability. (DTX-112.)

[9] And Dr. Klibanov pointed out that there are many ways to create extended release formulations

As to the second statement about the prodrug approach and simple crushing, whether or not it is correct, there is no evidence of record that a POSA would have believed in 2003 that a characteristic of prodrugs is that they cannot be cleaved by simple crushing of tablets. To support the crushing statement, Norwich cites the testimony of Drs. Mallamo and Klibanov, but neither one persuades that a prior art POSA would have known or believed this.[10] If such evidence existed, Norwich would have pointed it out clearly, and the prodrug solution to the d-amphetamine abuse problem might start to look obvious; Norwich has not done so, and the evidence shows that the inventor testified to a very different view. Defendant's statements on page 8 of its brief, which attempt to link extended release formulations, the d-amphetamine abuse problem, and prodrugs, are not supported by the evidence.

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that are not affected by crushing, but are not prodrugs. (Tr. 669:2-25.) Dr. Klibanov testified, persuasively, about such formulation-based approaches to abuse resistance: "the benefit of doing that is that you don't create a new chemical entity with all the uncertainty associated with it." (Tr. 669:6-7.) Dr. Klibanov stated that he was an inventor on a patent for such an abuse-resistant formulation of an opioid medication. (Tr. 669:22-25.) In contrast, Dr. Mallamo stated that he had never been involved with an attempt to reduce abusability through formulation. (Tr. 147:18-21.)

[10] Dr. Mallamo stated that there was no evidence that hitting a prodrug tablet with a hammer would break the amide bond. (Tr. 99:17-25.) Dr. Klibanov agreed that "a POSA would have known at the time that crushing a tablet would not result in breaking the amide bond in a Prodrug." (Tr. 691:14-17.) Neither side cites any other evidence that this knowledge was in the prior art, and it is implausible that a POSA, before LDX was even conceived of (or, as Dr. McGough put it, "an uninvented, unavailable prodrug" (Tr. 476:6), would have imagined a crushing experiment on a pharmaceutical tablet that did not exist, comprising a prodrug that did not exist, and would have had a reasonable expectation of the outcome. As Dr. Mickle testified, some amide bonds were weak, and you would need to actually test the bond to know its strength. (Tr. 579:19-25.) The Court is persuaded by Dr. Mickle, whose opinion is more consistent with the general consensus among all the experts that the functional properties of prodrugs are unpredictable absent testing. Furthermore, Dr. Mickle stated that the strength of the LDX amide bond – strong enough to resist various attempts at chemical hydrolysis, as their testing revealed – was "not a characterization you can make generally," but a property discovered through testing. (Tr. 579:12-25.) Dr. Chyall also stated that it was surprising that the amide bond was so stable that it could not be cleaved chemically in their tests. (Tr. 752:12-15.)

The evidence, considered as a whole, supports the conclusion that Defendant's theory of the motivation to combine the prodrug with the d-amphetamine abuse problem is simplistic, has a problematic gap, does not account for all the evidence, and contains a number of mistakes. The bottom-line problem for Norwich is the motivation to combine the prodrug teachings with the problem to be solved, the abuse of d-amphetamine due to crushing, snorting, and injection. The law requires "the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007). Norwich has not shown that a POSA would have been motivated to combine the prodrug teachings with the d-amphetamine abuse problem. Norwich has shown that a POSA would have been motivated to do something to eliminate initial spiking in plasma concentration levels as a possible approach to the d-amphetamine abuse problem, and a prodrug approach was one option. What is missing is the link between the d-amphetamine abuse problem and the prodrug, the prior art suggestion that a prodrug might solve this particular problem. The fact that the prior art understood that prodrugs could eliminate initial spiking in plasma concentration levels does not suffice to bridge the gap between the problem and the prodrug as solution. Norwich offers some conjectures (Def.'s Br. at 8) about extended release formulations, prodrugs, and crushing, but they contain mistakes and are unsupported by the evidence of record or insufficiently supported.

Norwich largely relies on the testimony of Dr. Mallamo to build the bridge between the d-amphetamine abuse problem and the prodrug, but Dr. Mallamo only states his inferential conclusions that a POSA would have been motivated to combine various prior art elements. Dr.

Mallamo was mistaken on a number of points, mischaracterizing the teachings of prior art references or not providing citations in support to particular prior art references. In KSR, the Supreme Court held:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

550 U.S. at 418. Dr. Mallamo merely testified that a POSA would have had a reason to combine the known elements in the fashion claimed by the patent at issue, but he did not sufficiently or persuasively articulate the reasoning that supported it. Dr. Mallamo gave conclusions that a POSA would have combined one element with another, not persuasive analysis explicating the reason to combine the d-amphetamine abuse problem with a prodrug solution to that problem. It is not enough to have an expert testify merely that a POSA would have had a reason; the challenger must explain the "reason to combine the known elements in the fashion claimed by the patent at issue." Id.

Norwich has failed to prove, by clear and convincing evidence, the first step in its obviousness theory: a POSA would have been motivated to combine the d-amphetamine abuse problem with a prodrug solution.

2. The Promoiety Step

Even though the determination of Defendant's failure at the Prodrug Step means that Norwich cannot succeed in proving its obviousness case, the Court will consider the evidence in support of Defendant's case for the Promoiety Step. The discussion that follows is contingent on the proposition – just rejected by the Court – that a POSA would have had a motivation to

apply the prodrug technique to solve the d-amphetamine abuse problem.

At the outset, the Court observes that, while Defendant's brief largely presents a theory of obviousness based on a motivation to combine an l-lysine prodrug with d-amphetamine, it also contains clear statements that a prodrug composed of l-lysine and d-amphetamine would be obvious to try. The Court will address both approaches.

A second threshold issue concerns which claims and what limitations are at issue in the analysis that follows. Takeda has asserted a range of claims. All of these claims require LDX, but claim 2 of the '787 patent requires only the isolated compound, LDX; claim 1 of the '561 patent requires LDX in a composition with certain additional ingredients; a number of claims require a pharmaceutical composition comprising LDX, or a salt of LDX; still others require a method of treatment comprising administering LDX to a subject; and so forth. The Court begins by considering the most basic claim, claim 2 of the '787 patent, requiring only the isolated compound LDX. Much of the discussion in the parties' briefs concerns functional characteristics of LDX, particularly when used in pharmaceutical compositions and methods of treatment. Claim 2 of the '787 patent contains no express requirements for the functionality of the compound. Later on in this Opinion, the Court will separately discuss the obviousness of functional characteristics of LDX.

At the Promoiety Step, the Court considers whether a POSA, having decided to use a prodrug to attempt to solve the d-amphetamine abuse problem, would have found it obvious to select l-lysine as the promoiety for the prodrug, resulting in the compound, LDX. Norwich proposes two combinations of prior art references in support of its theory that a POSA would have found it obvious to select l-lysine as the promoiety: 1) PDR with Patrick; and 2) PDR with

Miller.

a. Patrick

The Patrick reference is in a chapter from a medicinal chemistry textbook published in 2001, which teaches about the use of prodrugs to accomplish various goals. (DTX-449.) In introducing the prodrug section, Patrick states: "When designing prodrugs, it is important to ensure that the prodrug is effectively converted to the active drug once it has been absorbed into the blood supply, but it is also important to ensure that any groups cleaved from the molecule are non-toxic." (DTX-449 at 239.) Although Patrick has a subsection titled, "Prodrugs to prolong drug activity," Norwich focuses on the subsection titled, "Prodrugs masking drug toxicity and side effects." (DTX-449 at 244.) Within that subsection, there is one example, less than a page long, that states:

> LDZ is an example of a diazepam prodrug which avoids the drowsiness side-effects associated with diazepam. These side-effects are associated with the high initial plasma levels of diazepam on administration, and the use of a prodrug avoids this problem. An aminopeptidase hydrolyses off a non-toxic lysine moiety and the resulting amine spontaneously cyclizes to diazepam (Fig. 10.39).

(DTX-449 at 246.) The text is followed by a chemical diagram of a process. (Id.) Norwich contends that a POSA would have been motivated to combine Patrick's LDZ example with d-amphetamine to create a d-amphetamine prodrug which reduces the high initial plasma levels. Norwich contends: "Patrick discloses that the prodrug LDZ was formed using the a known [sic] benzodiazepine intermediate of diazepam (i.e., the diazepam precursor) that cyclizes into diazepam after the prodrug is cleaved following administration." (DFOF ⁋ 86.)

At the outset, the Court observes that the cited example in Patrick says nothing about amphetamine abuse or drug abuse, nor any reasoning about the selection of l-lysine as a

promoiety. Although Norwich never uses the word, "recipe," it is apparent that Norwich views Patrick as like a cookbook with various recipes: the POSA picks the LDZ recipe, substitutes d-amphetamine as the main ingredient, and prepares LDX by following the recipe.[11] In short, the evidence does not support this, for many reasons. Among them is the fact that there is no evidence that a POSA would believe that you can just swap the main ingredient and follow a recipe to achieve the same *in vivo* effects. Furthermore, the evidence shows there are important differences between the reaction that Patrick discloses to produce the LDZ prodrug and the reaction proposed in this case, producing LDX. Dr. Klibanov explained:

> Q. And so what does Patrick teach about LDZ?
>
> A. Patrick teaches that the prodrug LDZ, whereby lysine -- L-lysine is linked to a precursor of the drug diazepam. Now, it's important to note that in LDZ, L-lysine is not attached directly to the drug itself. So in this respect, it is quite different from what we have in L-lysine-d-amphetamine, where L-lysine is attached to the drug itself. That is not the case here. Furthermore, L-lysine is able to be attached to the precursor of diazepam rather than diazepam itself only because the eight-member ring, which the Court can see in diazepam which is in the lower right corner of this slide, is opened up. And it immediately follows that this approach could not possibly work for d-amphetamine because d-amphetamine has no such ring to open up. Furthermore, LDZ must be first cleaved in the body, and then it must cyclize. But there is no such mechanism that is possible or even conceivable for L-lysine-d-amphetamine. So it just shows a profound difference between LDZ, on the one hand, and L-lysine-d-amphetamine on the other.

(Tr. 646:14-647:9.) Dr. Klibanov here points out important differences between Patrick's LDZ example and the facts of this case. The first difference concerns the fact that the prodrug is created not from the active molecule, but from a precursor. Norwich does not explain how a POSA would find it obvious to apply this to d-amphetamine with a reasonable chance of success.

[11] As will be established, Patrick does not even teach the preparation steps of a recipe: it discloses no method of synthesis for LDZ.

How is the precursor selected? How does the POSA adapt this process for use with an unknown precursor compound that may not have an eight-member ring, which diazepam has but d-amphetamine does not have? (PFOF ¶ 208.) To return to the recipe analogy, Dr. Klibanov has explained that the Patrick recipe does not fit the d-amphetamine ingredient.

Moreover, the parties argued twice at trial about whether Dr. Mallamo would or would not present a theory of the synthesis of the LDZ prodrug, and counsel for Norwich twice declared affirmatively that Dr. Mallamo did not, and would not, describe the entire synthesis process for the LDZ prodrug in Patrick:

> MR. LANDMON: He is not, just to be clear, he is not going through a whole description of synthesis process per se. He is explaining what Patrick has shown of how you make the LDZ prodrug.

(Tr. 66:8-11.)

> MR. ROPER: Your Honor, I'm hearing him not actually quote from the report. I think that's what's telling. I think he's taking different half sentences here and there. If he has a specific quote he wants from the report about how it's actually synthesized, I don't think it's described in the report how LDZ is synthesized.
> MR. LANDMON: You're right.

(Tr. 67:16-22.) The testimony proceeded in accordance with counsel's commitments: Dr. Mallamo did not describe the entire synthesis process for the LDZ prodrug in Patrick. Nor did he explain how a POSA would have modified the teachings of Patrick to arrive at a synthesis process for LDX, taking into account the similarities and differences, such as the fact that Patrick's example begins with a precursor to the active drug rather than the active drug itself, and d-amphetamine lacks the eight-member ring that the diazepam precursor has. Nor did Dr. Mallamo make a case for how a POSA, applying Patrick to d-amphetamine, would have had a reasonable expectation of success in forming LDX.

Instead, as instructed by the Court, on the stand, Dr. Mallamo read parts of his expert report:

> So, "As discussed above in Section XIII.D, a POSA would also know that the diazepam benzodiazepine precursor, shown in the middle of the top row of Figure 10.39, and dextroamphetamine share common features such as an aromatic moiety and derivatizable primary amine group. The amide linkage between the amine group and the lysine molecule is driven by the lack of available derivatizable functional groups on diazepam itself and the available primary amine, glycyl alpha-amino group, on the well known diazepam benzodiazepine precursor. A POSA would know that forming an amide linkage is the most straightforward reaction with the carboxylic acid functional group available on lysine, as in the case of dextroamphetamine. Moreover, the amide bond is the common type of bond that forms between amino acids in a polypeptide, and is therefore the most likely to be the type of bond that would be the substrate for enzyme on the bodies, would normally act in this type of polypeptides. That's not in my text. A POSA would have therefore expected that conjugating L-lysine to dextroamphetamine would similarly hydrolyze off the non-toxic lysine moiety at a rate-dependent manner to release the active, thus reducing the initial plasma level spikes of dextroamphetamine, and therefore 'mask the drug's toxicity and side effects' associated with dextroamphetamine alone.

(Tr. 72:21-73:21.) Again, the Court notes that the analysis begins not with the active drug, diazepam, but with some precursor, and Dr. Mallamo does not explain how a POSA would have adapted such a synthesis process to d-amphetamine. Demonstrative exhibit DDX-213 shows this clearly: it shows a diazepam precursor – not diazepam itself – added to the l-lysine promoiety to produce LDZ. Norwich laid no foundation about precursors to d-amphetamine. Instead, the proposed Findings of Fact state:

> 92. A POSA would have understood that the diazepam compound itself does not have any functional groups, such as a primary amine group, that are available to readily react and form a derivative compound. Tr. 70:19-71:25 (Mallamo); DTX-449-30 (Figure 10.39).
>
> 93. Due to this lack of available functional groups on diazepam itself, a POSA would have understood that Patrick's strategy for forming a prodrug of diazepam utilizes the available primary amine on the well-known diazepam precursor because the precursor will spontaneously cyclize to regenerate diazepam after the

> lysine moiety is removed in the body. Tr. 70:11-21, 71:4-15 (Mallamo); DTX-449-30.

The cited testimony of Dr. Mallamo does state that the diazepam molecule lacks needed functional groups which are present in the precursor molecule. The Court finds Dr. Klibanov's objections credible and inquires: if diazepam lacks necessary functional groups, such that the POSA would need to find some other molecule with the necessary functional groups to modify, how would it be obvious to apply this to d-amphetamine? Norwich provides no explanation.

At bottom, as to the theory of obviousness based on combining the PDR with Patrick, the Court is presented with the conflicting testimony of two experts and finds Dr. Klibanov's testimony more credible and persuasive. The experts did not dispute the structural differences between diazepam and d-amphetamine, nor the structural and functional differences between LDZ and LDX. Dr. Klibanov looked at those differences and concluded that the concept in Patrick's LDZ example would not work with d-amphetamine. Dr. Mallamo looked at those differences and did not explain why a POSA would have found to obvious to modify the example of Patrick to apply it to d-amphetamine. The Court finds that the testimony of Dr. Klibanov deserves greater weight, and that the testimony of Dr. Mallamo is not sufficiently persuasive. Furthermore, it is undisputed that Patrick does not teach a method of synthesis for LDZ. In short, Norwich has not persuaded that a POSA would have understood how to modify the teachings of Patrick and apply them to d-amphetamine to form LDX with a reasonable expectation of success.

b. Miller's mistake

The second prior art combination proposed by Norwich consists of the PDR and the Miller reference. Miller is U.S. Patent No. 3,843,796, issued on October 22, 1974. (DTX-

573.) Miller teaches the creation of prodrugs of a drug named metaraminol. Norwich contends that a POSA would have been motivated to apply the teachings of Miller to d-amphetamine, with a reasonable expectation of success in forming LDX. Again, Norwich appears to treat Miller as a recipe for a genus of prodrugs, with the view that d-amphetamine can be substituted for metaraminol.

While there are many details to explore about Defendant's use of Miller to prove obviousness, the one that calls out for attention first is Miller's mistake. Norwich contends: "Example 5 of Miller discloses a two-part synthesis of the L-lysine metaraminol prodrug." (DFOF ¶ 137; DTX-573 at col.9.) Dr. Mallamo testified on this subject as follows:

> Q. Is there an example in Miller that discloses the process for synthesizing a prodrug of L-lysine?
>
> A. Yes, it does.
>
> Q. Is that Example 5?
>
> A. Example 5.
> . . .
> Q. Can you explain for us what Example 5 is disclosing?
>
> A. So he presents a two-part synthesis. In Part A, he is preparing the fully masked lysine metaraminol adduct. When I say "masked," what I mean is these two groups shown here in yellow, these are purposely put on lysine in order that we can direct the reaction to the amino group of metaraminol, rather than have lysine react with itself. So we mask those two groups. Now we can connect the two metaraminol in such a way that it can only react to the metaraminol amine generating the bond shown in red. We know -- we put these on purposely because we know we can remove them selectively at will.
>
> Q. So that was Part A of Example 5.
> MR. LANDMON: If we can turn to your next slide.
> BY MR. LANDMON:
> Q. Can you walk us through what he discloses in Part B?
>
> A. Yes. So Part B is where he has removed the terminal -- protecting group on the

terminal amino of lysine, as shown here in the green circle, leaving on the benzoyl protecting group.

Q. Is that protecting group also removable by a POSA?

A. Yes, it is.

(Tr. 77:20-78:25.) Dr. Mallamo thus understood Example 5 to disclose the synthesis of a l-lysine prodrug of metaraminol.

Dr. Klibanov pointed out that Miller's Example 5 contains a mistake:

Q. Are you aware that Miller has a number of numbered examples?

A. Yes, there are -- to be specific, there are 32 numbered examples in Miller. Most of them feature acylated amino acids as promoieties as opposed to free amino acids and conspicuously, none as I will explain more in detail, none features free L-lysine.

Q. Does Miller provide any preference for acylated molecules in addition to what you've discussed?

A. It does and expressly so. And in fact, the third bullet point on this side, which is a quote from Miller, specifically says: It is preferred that the above reaction, which is a prodrug formation, can be carried out on an acylated derivative of the amino acid as a promoiety rather than the free amino acid such as L-lysine would be.

Q. And then I wanted to turn to Example 5. Do you recall Dr. Mallamo's testimony that he believed Example 5 contains the free L-lysine?

A. Yes, I do recall it, and I disagree with his analysis.

Q. And can you explain why you disagree with his analysis?

A. Sure. So the title of Example 5 is indicated in the first bullet point. It's a complex chemical name; I will not read it. What matters is what I indicated in the red, which is in parentheses, which says -- and I read, N2 L-lysinamido. When the person of ordinary skill in the art looks at this parenthetical, he or she will understand that it makes no sense because N2 is an indication of which amino group in lysine is modified, but it doesn't say what it is modified with. So a person of ordinary skill in the art would understand that there must be a typographical error in this portion of the title, and specifically that the word

> benzoyl is missing right after N2. So that this is not a free L-lysine promoiety. And indeed, if one goes to the end of Example 5 in the compound that is called example -- called 5B, which is the last two lines on the right-hand side of this slide, it expressly states that the name of the compound correctly is N2 -benzoyl-L-lysinamido. So if you compare that with what was in the red on the left-hand side, it correctly states it's N2 -benzoyl. Therefore, one of skill in the art reading the Miller reference in its entirety would understand that, in fact, what is indicated -- what is produced in this example is acyl-lysine. So there is no free lysine promoiety in Example 5, contrary to what Dr. Mallamo indicated. Neither is there an express teaching or Miller does not provide a motivation to remove the N-acyl group from the promoiety. So the promoiety in Example 5 is acylated lysine, not free lysine itself.

(Tr. 656:15-658:16.)

Counsel for Norwich questioned Dr. Mallamo during direct examination about Dr. Klibanov's opinions about Example 5:

> Q. Now are you aware that Dr. Klibanov has been asserting that the end product of Example 5 is not the free L-lysine prodrug of metaraminol?
>
> A. Yes.
>
> Q. Would that have discouraged a POSA from using L-lysine as a prodrug moiety?
>
> A. No.
>
> Q. Why not?
>
> A. Well, we are demonstrating here the technology from much earlier, 1974. And at the time, and even now, we know we can add or remove these protecting groups as needed. So he is presenting here what's called a formal total synthesis where you name the compound. Chemists know how to take what you put at Part B, at the end, and convert it into the named compound by standard chemistries in the literature.

(Tr. 79:13-80:2.)

As these quotes show, Dr. Klibanov testified that Example 5 has a mistake, that a POSA would recognize the mistake and understand that Example 5 does not involve a free lysine

promoiety. Crucially, Defendant's proposed Findings of Fact concedes the point by proposing the following Findings:

> 143. A POSA would understand that the N2 in the title compound of Example 5 is a typographical error. Tr. 657:20-22 (Klibanov).
>
> 144. A POSA would understand that inclusion of the N2 in the title compound of Example 5 "makes no sense" because "it doesn't say what it is modified with." Tr. 657:13-179 (Klibanov).

The Court concludes that Norwich has conceded that Miller's Example 5 contains a mistake that a POSA would recognize. The Court also finds that Dr. Mallamo failed to recognize this mistake. The Court also finds that, when the mistake was pointed out to Dr. Mallamo, he did not disagree about it or rebut it. Therefore, the Court concludes that Miller's Example 5 does not teach the synthesis of a prodrug of metaraminol with a promoiety of l-lysine.

These determinations lead to others. Dr. Mallamo's opinions about Miller are based on a failure to recognize and understand a mistake in Miller, a mistake that a POSA would have recognized. As a result of this mistake, Dr. Mallamo incorrectly believed that Miller Example 5 taught the synthesis of a prodrug of metaraminol with a promoiety of l-lysine. Dr. Mallamo based his opinions on the teachings of Miller on an erroneous misunderstanding of Miller. Norwich did not rebut Dr. Klibanov's testimony on these subjects and, to a significant extent, conceded that Dr. Klibanov was correct. The Court determines that Dr. Mallamo's testimony on the subject of the Miller reference is defective due to these errors and deserves little weight.[12]

[12] Furthermore, Dr. Mallamo was blithe about the differences between metaraminol and d-amphetamine in the context of Example 5, involving protecting groups, saying only, "we can add or remove these protecting groups as needed." Dr. Mallamo did not explain why a POSA would have been motivated to add or remove particular protecting groups. As Takeda points out, in Shire, the Federal Circuit stated: "The problem for defendants is that example 24 is a final product, not an intermediate synthesis product. Defendants therefore have to show a reason why

The Court determines that Dr. Klibanov's testimony on the subject of the Miller reference is supported by the record and deserves great weight.

Dr. Klibanov and Takeda raised another question about Dr. Mallamo's opinions about the Miller reference. On the stand, Dr. Mallamo was questioned about demonstrative exhibit DDX-240, which shows part of Miller's Formula II:

> Q. So if we can have DDX-240 up. Can you walk us through quickly the main disclosures from these references that you relied on?
>
> A. So in the PDR, we see very apparently that dextroamphetamine is the most common component that is present in every amphetamine-presenting drug that is used to treat ADHD. So selecting dextroamphetamine as a lead molecule here is relatively straightforward. And it has with it an associated side effect that the literature is telling us that is addressable through this technology. So -- and that side effect is a single limiting principal factor in the medical utility of this drug. Miller then looks at this earlier with a drug of their interest which, in that case, the single limiting medical utility for this antihypertensive agent was the fact that it produced this rapid-onset side effect which could be potentially fatal. So he addressed that problem which is pharmacokinetically driven through attachment of a lysine residue in this case again, resulting in a time-dependent release from this what I call a covalent formulation.
>
> Q. Thank you, Doctor.

(Tr. 123:12-124:7.) On cross-examination, Dr. Mallamo took responsibility for the content of DDX-240 and admitted that there was more to Miller's Formula II than was shown on DDX-240, that DDX-240 did not show Miller's disclosures of the preferred compounds of Formula II, and that none of the preferred compounds of Formula II included free lysine. (Tr. 159:9-161:13.) Dr. Klibanov confirmed this understanding of Miller's Formula II: "Dr. Mallamo's Miller

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one of skill in the art would decide to start with example 24 and remove the protecting group. They have shown no such motivation." Shire, LLC v. Amneal Pharm., LLC, 802 F.3d 1301, 1308 (Fed. Cir. 2015). Nor has Norwich here shown why a POSA would start with the final product of Example 5 and remove the protecting group.

reference expressly prefers acylated amino acids, not free amino acids . . ." (Tr. 670:14-15.)

The Court notes two aspects of this. First, as to the content of DDX-240, which Dr. Mallamo took responsibility for, the demonstrative exhibit omitted important information about Formula II, that there was a statement of express preference for acylated amino acids rather than free ones. Second, as to Dr. Mallamo's understanding of the teachings of Miller, Dr. Mallamo omitted the express preference for acylated amino acids stated by Miller, and this greatly weakens Dr. Mallamo's case that Miller teaches formation of a prodrug using l-lysine. The evidence indicates that, while Miller does teach formation of a prodrug using l-lysine, among various options, Miller expressly prefers the use of an acylated l-lysine promoiety, and neither Norwich nor Dr. Mallamo explained why a POSA would have disregarded that statement of preference.

Dr. Klibanov also challenged Dr. Mallamo after Dr. Mallamo cited one of several Pochopin studies (DTX-467) in support of his view that a POSA would have selected l-lysine over d-lysine. (Tr. 115:22-117:13.) In that testimony, Dr. Mallamo referred to demonstrative exhibit DDX-234, which quotes a paragraph from the DTX-467 study. (DDX-234, quoting DTX-467 at 774.) Dr. Klibanov pointed out that that paragraph could be read to support the opposite conclusion, since it does state that d-amino acid prodrugs have longer residence times *in vivo*, and there is no dispute that the POSA would have intended the prodrug to slow the *in vivo* release of d-amphetamine. (Tr. 671:22-672:7; DTX-467 at 774.) Dr. Klibanov also noted that this Pochopin reference stated that derivatives with longer residence times "may be useful for sustained release." (Tr. 672:3-7; DTX-467 at 774.) In this example, Dr. Mallamo was not wrong, but his testimony did not completely and accurately reflect the more complex and mixed

nature of the underlying evidence, which Dr. Klibanov pointed out; Dr. Mallamo disregarded a statement in Pochopin that could be understood to teach away from the use of an l-lysine promoiety.

Dr. Klibanov also challenged Dr. Mallamo as to two Biel references: "the Biel 1972 and 1975 articles, both of them reference -- both of them illustrate the use of D-amino acids, and specifically D-lysine, rather than L-lysine." (Tr. 672:12-673:13, citing DTX-572 and DTX-574.) The text of the references supports Dr. Klibanov. (DTX-572 at col.1 l.49; DTX-574 at col.2 ll.57-59.)

These findings damage Dr. Mallamo's credibility as a witness, and also reduce the weight his opinions will be given. Dr. Klibanov's understanding of the prior art references was supported, increasing the weight his opinions will be given.

The Court concludes that a POSA would not have been motivated to combine the teachings of either Patrick or Miller with the PDR, and thus would not have been motivated to modify d-amphetamine to produce LDX.

As to the expectation of success in producing the LDX compound, Defendant's brief states only:

> a POSA would have reasonably expected to be able to form LDX, and that LDX would work like the prodrugs in Patrick and Miller and release d-amphetamine in the body in a slower manner. NFOF ¶¶ 488-90, 494, 498, 501, 529, 536-38, 541-45.

(Def.'s Br. at 12-13.) Of the cited proposed Findings of Fact, here are the ones relevant to the formation of LDX:

> 489. A POSA would have had a reasonable expectation of successfully developing the prodrug L-lysine-d-amphetamine because both Patrick and Miller disclose successful examples of forming lysine prodrugs. Tr. 120:11-19

(Mallamo); DTX-449-30; DTX-573.

494. A POSA would have had a reasonable expectation of successfully developing the prodrug L-lysine-d-amphetamine because they would know that dextroamphetamine has an available primary amine group like both of the drugs disclosed in Patrick and Miller. Tr. 120:11-22 (Mallamo); DTX-449-30; DTX-573.

498. A POSA would have had a reasonable expectation of successfully developing the prodrug L-lysine-d-amphetamine using an amide bond because dextroamphetamine has an available primary amine group and lysine has an available carboxylic acid group. Tr. 120:11-121:4 (Mallamo).

501. Based on the disclosures of the prior art, a POSA would have reasonably expected that "conjugating L-lysine to dextroamphetamine would similarly hydrolyze off the non-toxic lysine moiety at a rate-dependent manner to release the active, thus reducing the initial plasma level spikes of dextroamphetamine," and therefore prevent or reduce the pharmacokinetically driven side effects (i.e., euphoria) associated with administration of dextroamphetamine alone. Tr. 73:15-21 (Mallamo).

537. A POSA would have been motivated to and had a reasonable expectation of developing an L-lysine prodrug of dextroamphetamine because Miller discloses a metaraminol prodrug created by forming a routine amide bond between lysine and the drug compound as described in Formulas 1 and 2 and Example 5 of Miller. Tr. 126:8-20 (Mallamo); DTX-573-2-3, -6.

These proposed Findings of Fact cite only the testimony of Dr. Mallamo and the Miller and Patrick references. The Court has rejected key aspects of Dr. Mallamo's opinions about Miller and Patrick, and has decided to give his opinions in this area little weight. The opinions of Dr. Klibanov have been given great weight. Norwich has not proven that a POSA would have had a reasonable expectation of successfully forming the compound L-lysine-d-amphetamine.

c. The alternative obvious-to-try theory

Norwich also contends that a POSA would have been motivated to attach a promoiety to the amino group of d-amphetamine, and that it would have been obvious to try l-lysine. (DFOF ¶ 430.) Curiously, although Norwich clearly states that it proposes an "obvious to try" theory,

Defendant's post-trial brief cites no authority about the "obvious to try" inquiry, nor does it offer any argument to persuade that it has satisfied the legal requirements for an "obvious to try" theory to succeed. The Court, nonetheless, knows the applicable law, and will apply it to the case as best it can:

> To prove obviousness under an obvious to try theory, [the challenger] must show (1) a design or market need to solve a particular problem, *and* (2) that "there are a finite number of identified, predictable solutions" that would lead to an expectation of success. *KSR*, 550 U.S. at 421 (emphasis added).

Grunenthal GmbH v. Alkem Labs. Ltd., 919 F.3d 1333, 1345 (Fed. Cir. 2019). The first element, a design or market need to solve a particular problem, has already been established. Norwich must demonstrate the second element. The Court is at a loss, however, to figure out Norwich's position as to the "finite number of identified, predictable solutions," since the brief does not address the issue. The Court is left to guess what Norwich contends is the finite number, and there are two bits of information. First, Defendant's proposed Findings of Fact points to Dr. Mallamo's testimony on the subject, in which he gives reasons why a POSA would have selected l-lysine from a set of twenty candidates composed of the twenty naturally-occurring amino acids. (Tr. 113:7-117:13.) L-lysine is the only promoiety Dr. Mallamo or Norwich identifies as obvious to try. Second, the brief has a footnote which states: "Norwich has pointed to evidence supporting the inference that a small group of L-series amino acids, one of which is L-lysine, are solutions to the problem of providing a d-amphetamine prodrug." (Def.'s Br. at 11 n.5.) Which is that small group? The 20 amino acids in Miller? The 3 amino acids Dr. Mallamo picked out of the twenty before he picked l-lysine? Norwich does not explain.

The footnote indicates that Norwich contends that some group of amino acids are

solutions. The problem here is that Norwich does not even attempt to persuade that an l-lysine prodrug meets the requirement of being an identified, predictable solution – much less that there is a group of amino acids that are identified, predictable solutions. It is undisputed that the prior art did not disclose LDX, and the record contains no evidence that anyone had identified a d-amphetamine prodrug in which l-lysine is attached to the amino group as a solution to the problem of d-amphetamine abuse. Nor does the record show that anyone in the prior art had identified any prodrug as the solution to any problem involving the abusability of drugs.[13] The Court finds that Norwich has not proven that LDX would be obvious to try.

D. The obviousness of salts

The Court has determined that Norwich has failed to prove that the compound LDX was either obvious or obvious-to-try. Because every other claim at issue requires LDX, Norwich cannot prove that any asserted claim is obvious. Nonetheless, the Court will make some determinations specific to the salt claims, and to the claims which involve prodrug functionality. Norwich contends that the claims which recite a "pharmaceutically acceptable salt" of LDX are obvious, as are claims requiring a mesylate salt or a dimesylate salt of LDX. Norwich argues

[13] Defendant's post-trial brief does not make any argument based on Piccariello and Kirk. Piccariello is a named inventor on the asserted '787 patent. Defendant's proposed Findings of Fact asserts that Piccariello and Kirk is prior art to the asserted patents (DFOF ¶ 302), while Takeda disagrees (PFOF ¶ 320.) The Court need not reach this dispute because Norwich does not reference Piccariello and Kirk in its brief; nor did Defendant's pre-trial brief mention the reference. In any case, given the date of publication of the reference, September 4, 2003, and the parties' agreements on the Priority Dates of the asserted patents, Piccariello and Kirk could not be prior art to claim 12 of the '735 patent, claim 1 of the '630 patent, claims 4 and 25 of the '030 patent, claim 4 of the '486 patent, claim 7 of the '031 patent, and claim 5 of the '770 patent. Nonetheless, Piccariello and Kirk was admitted into evidence, was a subject of testimony at trial, and appears to be the only reference of record to identify a prodrug as a solution to a problem with the abusability of a controlled medication.

for a reasonable expectation of success only for the dimesylate salt. Because the dimesylate salt is a species within the genus of mesylate salts and also within the genus of pharmaceutically acceptable salts, Norwich need only demonstrate the obviousness of the dimesylate salt to succeed. In re Cuozzo Speed Techs., LLC, 793 F.3d 1268, 1281 (Fed. Cir. 2015) ("It is a long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter.")

There is no dispute that salt forms of medications are common, and that chemical reactions that result in salt forms are common and well known in the art of pharmaceutical development. The issue turns on the question of whether a POSA would have a reasonable expectation of success in creating the dimesylate salt of LDX.

Norwich relies on the testimony of Dr. Sloan to prove that a POSA would have a reasonable expectation of success in creating the dimesylate salt of LDX. Dr. Sloan was offered and admitted as an expert in the fields of organic and medicinal chemistry, including selection of salt forms of pharmaceuticals. (Tr. 211:12-23.) Dr. Sloan did state the conclusion that a POSA would have a reasonable expectation of success in creating the dimesylate salt of LDX. (Tr. 243:23-25.) The Court finds that Dr. Sloan is not credible and his testimony will be given no weight, for several reasons. First, on cross-examination, Dr. Sloan admitted that he had never performed a salt screen or worked with a dimesylate salt. (Tr. 265:12-22.) As the same time, Dr. Sloan opined that a POSA would routinely perform a salt screen, and so he does not meet his own definition of a POSA. (Id.) The Federal Circuit has held:

> To offer expert testimony from the perspective of a skilled artisan in a patent case—like for claim construction, validity, or infringement—a witness must at least have ordinary skill in the art. Without that skill, the witness' opinions are neither relevant nor reliable.

Kyocera Senco Indus. Tools, Inc. v. ITC, 22 F.4th 1369, 1376-77 (Fed. Cir. 2022). On this basis alone, it is proper to exclude Dr. Sloan's testimony on any salt-related topic.

There are additional reasons to question Dr. Sloan's credibility. First, Dr. Sloan agreed that, after his deposition, counsel for Norwich wrote to counsel for Takeda: "We write to inform you that Dr. Sloan misspoke today during his deposition when he indicated that he reviewed drafts of Dr. Mallamo's opening report." (Tr. 276:25-277:9.) Second, Dr. Sloan testified at trial on lack of enablement of the salt claims in the patents at issue. (Tr. 251:4-5.) On cross-examination, Dr. Sloan was questioned about two patents, for which he is sole inventor, with claims requiring "pharmaceutically acceptable salts," but which do not disclose how to make any salts, and he stated that those claims are not enabled, although he has not yet informed the PTO of this. (Tr. 267:14-271:12.) The Court observed Dr. Sloan's demeanor carefully during this cross-examination and did not find him credible: certainly his testimony that the claims of his own patents were not enabled did not appear credible.

Third, Dr. Sloan's testimony on salt selection was inconsistent with statements on cross-examination. Dr. Sloan laid this foundation, here quoted in part, for his opinions on salt selection:

> Q. Would a POSA, as of May 29, 2003, agree that dissolution rates are typically greater in salts?
>
> A. Yes, they would.
>
> Q. Earlier on that page there is a clause that reads: It is usually better to formulate with a salt. Would a POSA agree with that statement as of May 29th, 2003?
>
> A. Yes.
>
> Q. Why is that, Dr. Sloan?

> A. Well, again, you would want the molecule to dissolve, the salt form in this case, to dissolve quickly so that you can get faster absorption and -- before the drug or the salt form in this case clears the body.

(Tr. 217:22-218:9.) Dr. Sloan agreed that a "POSA would have had a reasonable expectation of successfully pursuing a pharmaceutically acceptable salt of LDX" as well as a mesylate salt. (Tr. 223:16-18; 241:5-7.) On cross-examination, Dr. Sloan stated that he began his analysis of salt selection in this case without any information about the properties of LDX free base; he did not know anything about its hygroscopicity or solubility, nor whether it needed higher or lower solubility. (Tr. 277:23-278:20.) Dr. Sloan agreed that the hygroscopicity and solubility of a compound have interactive effects and affect other compound characteristics, such as stability. (Tr. 278:21-280:18.) Dr. Sloan stated:

> Q. And if you increase solubility in many cases would you would increase the tendency to be hygroscopic, correct?
>
> A. It could.
>
> Q. It's not just that it could. If you increase solubility in many cases you would increase the tendency to be hygroscopic, correct?
>
> A. Yes.
>
> Q. And an increase in hygroscopicity would generally result in a decrease in stability, correct?
>
> A. Okay. Say that again.
>
> Q. An increase in hygroscopicity would generally result in a decrease in stability, correct?
>
> A. Correct.

(Tr. 279:4-16.) Thus, Dr. Sloan's obviousness analysis on direct examination omitted relevant facts about pharmaceutical salt selection he knew to be true. His opinions did not take account

of those relevant facts, and Dr. Sloan was willing to express opinions despite not knowing key facts about the hygroscopicity and solubility of LDX free base. Here is one specific example of how this is problematic: Dr. Sloan began his testimony with the premise that dissolution rates are typically greater in salts, but admitted on cross-examination that increasing solubility "in many cases" would decrease stability. Dr. Sloan's conclusions from such reasoning cannot be credited.

For all the reasons stated, the Court concludes that Dr. Sloan's testimony is not credible and no part of it will be given any weight. This determination leaves Norwich with no evidence from Dr. Sloan to support its arguments that the claims at issue with salt limitations are invalid due to obviousness. Norwich tries unpersuasively to argue that Dr. Chyall made key admissions, particularly as to predictability. Norwich points to this testimony:

> Q. Dr. Chyall, would a skilled person be able to predict whether a salt will form from an acid-base reaction such as the one you've illustrated here?
>
> A. In solution, yes. This proton transfer reaction is highly predictable. We know the strengths of these acids from other studies, and even if you don't have any knowledge of the compound, the functional group, the amine functional group is enough for a skilled person to know that this reaction will occur.

(Tr. 717:12-20.) Dr. Chyall did state that the proton transfer reaction is highly predictable: the POSA can predict whether the salt formation reaction will occur. Dr. Chyall did not state that the properties of the resultant salt are predictable. The two are very different.

Norwich contends:

> Dr. Chyall opined that a "pharmaceutically acceptable" salt could be made and used simply by using an acid that "in theory could be used as a pharmaceutical." NFOF ¶ 612.

(Def.'s Br. at 24.) The cited proposed Findings of Fact states:

> 612. According to Dr. Chyall, "pharmaceutically acceptable" in the context of the asserted claims reciting "a pharmaceutically acceptable salt" of LDX means that the acid providing the counterion used in forming the salt is something that in theory be used as a pharmaceutical. Tr. 758:4-9 (Chyall).

The Court finds that Norwich has cherry-picked Dr. Chyall's testimony in the service of a belated claim construction argument. Dr. Chyall also stated that "pharmaceutically acceptable" in the context of the claims means "something that has a potential to be commercialized." (Tr. 757:15-25.) The flow of the questions and answers in the trial transcript suggests that Dr. Chyall was uncertain how to precisely define "pharmaceutically acceptable." In any case, the Court decides the meaning of particular claim terms as a matter of law; it is not a factual matter for trial. Markman v. Westview Instruments, 517 U.S. 370, 372 (1996). Neither party requested claim construction of the term, "pharmaceutically acceptable salt." The Court rejects this belated attempt to cabin the meaning of "pharmaceutically acceptable salt" in a post-trial brief based on cherry-picking statements of an expert. The Court weighs Dr. Chyall's testimony as to matters of fact, not matters of law. As already stated, Dr. Chyall testified that a POSA could predict whether the salt formation would occur but could not predict the properties of the resultant salt. Moreover, Dr. Chyall provided this foundation for his testimony on salt selection:

> Salt screening is where you take your compound of interest and you have identified problems with it, and now you have to examine the salt forms of that compound through experimentation. So that involves setting up a whole variety of experiments with various acids and getting results to understand what of those salts could potentially then be taken further on into the development process.

(Tr. 726:6-12.) Dr. Chyall did not opine that a POSA, presented with a compound of interest, would be motivated to create a pharmaceutically acceptable salt, or would have a reasonable expectation of success at the end of the "whole variety of experiments."

Moreover, Dr. Chyall expressly stated that the properties of salt forms are not predictable.

Dr. Chyall first stated: "The Davies reference states: 'there is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity.'" (Tr. 729:7-22.) He then stated: "A POSA cannot predict properties of a salt based on a structurally similar compound, as the Davies reference shows." (Tr. 732:20-733:7.) Norwich has not persuaded the Court that Dr. Chyall's testimony supports finding that a POSA would have had a reasonable expectation of success in creating a particular pharmaceutically acceptable salt of LDX.

At times, Norwich seems to suggest that because it is generally likely that a far-ranging research effort would eventually turn up at least one pharmaceutically acceptable salt form of an unknown free base compound (even if a POSA could not predict in advance which one that will be), a claim reciting the genus of pharmaceutically acceptable salt forms of LDX is obvious. Federal Circuit law does not support this view. Norwich could succeed by showing that one specific species within the genus is obvious – like the dimesylate salt, for example – but it has not done so. Nobody testified that, before testing, a POSA would have had a reasonable expectation that LDX dimesylate – or some other identified salt form of LDX – would have the properties necessary for it to be pharmaceutically acceptable. Dr. Chyall's testimony supports the conclusion that a POSA could have predicted whether the proton transfer reaction between methanesulfonic acid and LDX would occur, but not whether the resultant dimesylate salt would be pharmaceutically acceptable.

Takeda points to the deposition testimony of one of Defendant's designated 30(b)(6) witnesses, Dr. Moghaddam, who testified about development of salt forms of LDX for Norwich. Dr. Moghaddam stated that the solubility, stability, and pharmacokinetics of a new salt form

cannot be predicted. (Tr. 552:10-553:6.) Moore's Federal Practice states:

> It should be kept in mind that a Rule 30(b)(6) designee testifies on behalf of the corporation, and binds the entity with its testimony. This means that a corporation generally cannot present a theory of the facts that differs from that articulated by the designated Rule 30(b)(6) representative.

7 Moore's Federal Practice - Civil § 30.25 (2022). Norwich is bound by Dr. Moghaddam's testimony and cannot present a theory of the facts that differs from it. Another Norwich 30(b)(6) designee, Dr. Fackler, testified that the choice of salt form can affect the pharmacokinetics achieved. (Tr. 568:9-11.)

Norwich, however, cites the Federal Circuit's decision in Pfizer, a case very much on point. In Pfizer, the Court held: "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007). Thus, in the instant case, pursuant to Pfizer,[14] obviousness cannot be avoided simply by showing unpredictability in the art of salt selection. Nonetheless, Pfizer does not hand Norwich the win on the obviousness of the salt claims. Pfizer teaches that the trial court must examine the evidence of the expectation of success – and the facts of Pfizer do not help Norwich. Id. ("The evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that an acid addition salt of besylate would form and would work for its intended purpose.") In Pfizer, the inventor had testified that, before doing the salt selection research, he drew up a list of seven salt forms of the compound of interest that he expected would form salts;

[14] What is particularly interesting about Pfizer is that, as to the principle for which Norwich cited it, it fits the instant case so well: it is very helpful in cautioning the trial court not to allow the finding of general unpredictability in the art of pharmaceutical salt selection to detract from focus on the key evidence of the POSA's reasonable expectations of success.

the besylate salt was one of them. Id. The inventor had further testified that he expected that the listed salts "might be a cure for the problems" he was having with developing a salt form. Id. at 1365. The Federal Circuit concluded that the prior art taught that the besylate salt would work. Id.

Norwich has not presented evidence that the inventors expected that any specific salt form would work as a pharmaceutically acceptable salt prior to testing. Nor has Norwich presented evidence that "would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that [a specific LDX salt] would form and would work for its intended purpose." Id. at 1364. The evidence of record only supports a finding that a POSA would not have had a reasonable expectation of success.

It is undisputed that the salt form of a neutral compound may be less stable than the neutral compound, which is undesirable for a pharmaceutical. The record contains no evidence that a POSA, presented with the previously unknown compound LDX, could predict the stability of particular salt forms of the compound, nor that a POSA would have reasonably expected particular salt forms to be either stable or pharmaceutically acceptable. Norwich is bound by the testimony of its 30(b)(6) designee that the stability and pharmacokinetics of a new salt form cannot be predicted, and there is no contention that a POSA in 2003 would have believed anything different. While the general process to create and research salt forms of pharmaceutical compounds was well known in the art, neither party contends that a POSA could reasonably expect in advance of testing that a particular salt form of a particular compound would be pharmaceutically acceptable. A POSA would not be motivated to develop a less stable form of a pharmaceutical, nor could a POSA have a reasonable expectation that a

particular salt form would show improved stability, or other properties of a pharmaceutically acceptable salt. Norwich has failed to prove that the claims at issue with salt limitations are invalid due to obviousness.

E. The obviousness of claims requiring *in vivo* prodrug functionality

1. In general

The last obviousness topic that the Court will address concerns all claims reciting limitations related to the *in vivo* prodrug functionality of LDX. This group includes claims with limitations as to pharmacokinetic parameters, such as AUC or T_{max}, and claims with limitations as to pharmaceutically effective amounts, methods of treatment, therapeutic effects, bioavailability, release of amphetamine, and the like. All such claims share a requirement that LDX function as a prodrug *in vivo*, releasing amphetamine in the body of a subject. As before, the discussion that follows is contingent on the propositions – already rejected by the Court – that a POSA would have had a motivation to apply the prodrug technique to the problem at hand, and that a POSA would have chosen l-lysine as the promoiety to arrive at the compound, LDX. If the POSA had arrived at the compound LDX, would that POSA have had a reasonable expectation of success in producing the *in vivo* prodrug functionality recited in the claims?

The evidence of record establishes that a POSA would not have believed, in the absence of testing, that the *in vivo* prodrug functionality of LDX was predictable in any relevant way. Given that the core of Defendant's theory of obviousness is the idea that a prodrug will moderate initial spiking in plasma concentration levels, the first question is: would a POSA have reasonably expected success in creating a prodrug form of d-amphetamine, with l-lysine as the promoiety, that moderated initial spiking in plasma concentration levels?

Norwich argues that a POSA would have reasonably expected that the prodrug formed from d-amphetamine and l-lysine would function like the prodrugs in Miller and Patrick, moderating initial spiking in the d-amphetamine plasma concentration curve. Norwich bases this on the alleged structural similarity of d-amphetamine to the relevant compounds in both Miller and Patrick. (Def.'s Br. at 12; DFOF ⁋⁋ 490-99, 517-19, 538-40; DDX-237, 238, 241, 243.) Takeda contends that a POSA would have known that, both in general and for prodrugs, structural similarity does not predict functional similarity *in vivo*.

The evidence of record supports Takeda's position on this point. Norwich relies primarily on the testimony of its expert, Dr. Mallamo. Dr. Mallamo testified extensively on the use of structural similarity to predict functional similarity *in vivo*. (See Tr. 119-128.) Takeda relies on the testimony of its expert, Dr. Klibanov.

The Court has already evaluated the credibility and the weight to be given to these experts in regard to the Miller and Patrick references. It now considers these questions as to their testimony about the *in vivo* functionality of prodrugs. For the reasons that follow, the Court again finds that Dr. Klibanov's testimony is more credible and deserving of greater weight than that of Dr. Mallamo.

Dr. Klibanov challenged Dr. Mallamo's use of structural similarity to predict functional similarity *in vivo*:

> Dr. Mallamo is correct that there are some significant similarities between the structures of d-amphetamine and metaraminol, but there are also some significant differences between the structures of the two compounds. Furthermore, it is well known that even structurally similar compounds, even if that were the case, can have markedly different pharmacological properties as is also confirmed by one of Dr. Mallamo's own references.
>
> Q. And the reference you are referring to is the Cavallito 1979 reference?

A. Yes.

(Tr. 652:4-14.) Cavallito states: "Examples abound of chemically similar compounds with markedly different pharmacological properties and dissimilar chemicals with comparable pharmacology." (DTX-118 at 23.) Cavallito supports Dr. Klibanov on this point and does not support Dr. Mallamo.

Dr. Klibanov also testified about the Hudkins article, on which Dr. Mallamo was a co-author, published in 1998. (Tr. 662:9-22; DFOF ¶ 343; PTX-636.) Dr. Klibanov stated:

> And in this study, Dr. Mallamo attempted to produce a prodrug where L-lysine was a promoiety, just like it is in L-lysine-d-amphetamine.
>
> Q. And what happened?
>
> A. And what he found here is that this L-lysine base prodrug was not stable, which forced Dr. Mallamo to switch to polypeptide base promoiety. So not only was it not L-lysine, it wasn't even a free mono amino acid, so again, basically pointing to the unpredictability and potential instability of prodrugs.

(Tr. 662:10-20.) Norwich argues that the study involved "a far more complicated molecule," which is beside the point. (Def.'s Br. at 14.) The Hudkins article is relevant here for its impeachment value: although Dr. Mallamo testified that a POSA, before the priority date, would have a reasonable expectation of success using l-lysine as a promoiety in a prodrug based on an analysis of structural similarity, he participated in a study, just five years earlier, in which the l-lysine prodrug did not manifest the expected characteristics, which Norwich did not dispute, and it had the opportunity to cross-examine Dr. Klibanov on the subject. Why did Dr. Mallamo fail to correctly predict the functional characteristics of interest of that prodrug? This is quite relevant to his credibility, particularly on the subject of the predictability of prodrugs with a promoiety of l-lysine, and provides further support for the determination that Dr. Mallamo's

testimony on the subject of the predictability of prodrugs with a promoiety of l-lysine is not credible and deserves little weight.

Norwich relies considerably on Dr. Mallamo's testimony to support its theory of the obviousness of claims relating to the *in vivo* functionality of prodrugs, but Dr. Mallamo's testimony about prodrugs had quite a few problems, many of them appearing from Dr. Klibanov's challenges. Dr. Klibanov critiqued Dr. Mallamo on the subject of the amide bond that attaches the promoiety to d-amphetamine. There is no dispute that, in LDX, that bond is an amide bond. (DFOF ⁋ 1313; PFOF ⁋ 660.) Dr. Mallamo stated: "The properties of this [amide] bond, including its chemical stability, would have been well-known to any POSA operating at the time." (Tr. 824:8-10.) Dr. Mallamo cited a Pochopin study in support of this assertion. (Tr. 824:21-25; DTX-466.) Dr. Klibanov critiqued Dr. Mallamo not discussing a different Pochopin reference, in which the authors attempted to use l-lysine as the promoiety for an amide prodrug of Prazosin, but found it to be unstable and that it rapidly degraded. (Tr. 663:9-21; PTX-1725.) Norwich did not dispute this characterization of that reference. Furthermore, the inventor, Dr. Mickle, stated: "There are certainly a number of very weak amide bonds that break apart fairly easily." (Tr. 579:19-21.) Dr. Mallamo's assertion about the stability of the amide bond was not entirely wrong, but it did not completely and accurately reflect the more complex and mixed nature of the underlying evidence, which Dr. Klibanov pointed out.[15]

Dr. Klibanov also critiqued Dr. Mallamo based on the Biel 1970 reference:

[15] Also, Dr. Chyall stated: "It is surprising and unexpected that Vyvanse® has an amide linkage so stable that it cannot be cleaved chemically to release abusable d-amphetamine, as discussed in the '630 patent." (Tr. 752:3-753:5.)

> And there was a text of the Biel 1970 reference that Dr. Mallamo did not mention which says that all of the structural elements of amphetamine are critical to its pharmacological and biochemical activity spectrum. And it adds: Any structural modifications, additions or subtractions will accentuate some of the actions, abolish or attenuate others, or uncover latent ones not previously demonstrable with the parent structure. And what that indicates to one of skill in the art is that any modification of a drug may or may not produce a viable prodrug as I will indicate in a moment on the next slide. . . So the next slide shows on the left-hand side, it shows the chemical structure of amphetamine which is noncontroversial. Dr. Mallamo indicated that if you modify this free amino group, NH2 group, you inactivate the drug, but that just isn't true. Because what is shown on the right-hand side is that if you take amphetamine and modify, chemically modify that amino group with a methyl group, which is a CH3 group, what you produce as a result is not a prodrug, not a viable prodrug, you actually produce another drug which is called methamphetamine which actually is a drug itself, so it's not inactive until cleaved. And furthermore, this particular drug methamphetamine in fact is a drug, not a very good one, but nevertheless, is an approved drug to treat ADHD.
>
> BY MR. ROPER:
> Q. Is it your view that a POSA would need to do testing to understand if a molecule will be inactivated?
>
> A. Without testing there is just no way to legitimately predict that.

(Tr. 665:3-666:11.)

Dr. Mallamo's testimony on the subject of prodrugs was also challenged on cross-examination. On direct examination, Dr. Mallamo testified that a POSA would have chosen an l-amino acid over a d-amino acid because there were safety concerns about using d-amino acids, which are not natural and are recognized less by enzymes in the body, and so might not cleave. (Tr. 116:24-117:13.) On cross-examination, Dr. Mallamo conceded that there was no reason not to use a d-amino acid and, in fact, a POSA would expect a d-amino acid to release more slowly, with a longer duration of action. (Tr. 169:17-171:5.) This reversal of position both damaged Dr. Mallamo's credibility and also tends to show that Dr. Mallamo's initially-stated theory is not correct.

The Court thus again finds that, on a few points, Dr. Klibanov persuasively pointed out that Dr. Mallamo was wrong or mistaken, while on a few others, Dr. Klibanov pointed out that Dr. Mallamo's opinions did not completely and accurately reflect the more complex and mixed nature of the underlying evidence. Cross-examination also effectively challenged a number of Dr. Mallamo's opinions. Dr. Klibanov's testimony was generally supported by the evidence of record and withstood cross-examination. The Court concludes that, on the subject of predicting the *in vivo* functionality of a prodrug, the testimony of Dr. Klibanov was more credible and more deserving of weight, while the testimony of Dr. Mallamo was less credible and less deserving of weight.

The Court has already discussed some of the evidence of the unpredictability of prodrugs. There is more of such evidence that relates to the unpredictability of the *in vivo* functionality of prodrugs. On cross-examination, Dr. Mallamo agreed that "you could have a prodrug that results in a shorter T_{max} and a higher C_{max} of amphetamine." (Tr. 172:12-14.) Takeda also challenged Dr. Mallamo about his deposition testimony about Patrick, in which Dr. Mallamo stated that Patrick does not disclose how long it takes to cleave the l-lysine group from the LDZ prodrug in the body, so it could be one minute or ten hours. (Tr. 155:13-157:10.) Thus, Dr. Mallamo essentially conceded that the timing of prodrug release of the active was unpredictable.

Furthermore, Dr. Taft's testimony supported the inference that the *in vivo* functionality of prodrugs is not predictable. Dr. Taft stated:

> Well, there is a number of complicated factors that are involved with a prodrug that wouldn't be predictable without testing and I have them listed here on the screen. For example, before testing you wouldn't have been able to predict whether L-lysine-d-amphetamine behaved like a prodrug or not. What I mean by that is you don't know whether it would convert in the body after it was administered. If it did convert, where is it converting? What is the rate and extent

> of that conversion because that relates directly to pharmacokinetics and bioavailability and other parameters.

(Tr. 788:17-789:1.) Dr. McGough presented a very similar opinion about the unpredictability of the *in vivo* functionality of prodrugs:

> prodrugs themselves can be unpredictable. It can be unpredictable if it is truly inactive when ingested. It is unpredictable as to whether it will be successfully cleaved and the manner in which it will be cleaved. It probably, with most importance, the rate and extent of release could be variable, as has been discussed in part and as I will discuss more.

(Tr. 476:15-22.) Dr. Mickle, one of the inventors, discussing early research in the development process for LDX, stated:

> Q. What was the outcome of the research?
> A. Eventually we learned that every prodrug is unique, that the amino acid attached to it, depending on what it is, is not predictive, that you can't use properties of the amino acid to determine how the prodrug is going to behave. It's entirely an empirical process.
> Q. You said that you can't use the properties of the amino acid to determine how the prodrug is going to behave. Why is that?
> A. If I knew the answer, it wouldn't be research. I would only have to make one molecule, so there is no way to predict once you prepare a molecule how it's going to behave.

(Tr. 577:14-25.)

Viewing the evidence as a whole, the Court finds strong support for two propositions: 1) the art, in general, believed that the *in vivo* functionality of prodrugs could not be predicted without testing; and 2) a POSA considering the LDX molecule would not have had a reasonable expectation of success as to finding that LDX manifests the claimed functional characteristics *in vivo*.

2. Claims with dosage limitations

Norwich contends that the dosage limitations, which appear in claims 1, 6, and 9 of the

'561 patent and claims 4 and 25 of the '030 patent, are obvious. All of these claims contain express limitations related to the *in vivo* functionality of the LDX prodrug, with the exception of claim 1 of the '561 patent, which claims only a particular pharmaceutical composition. A dosage of a pharmaceutical composition implies administration to a human subject: Norwich does not contend that a POSA would not understand the dosage range in the pharmaceutical composition of claim 1 to be premised on the expectation of administration to human subjects. The following analysis thus applies to claim 1 of the '561 patent as well as to all claims which expressly require *in vivo* functionality of the LDX prodrug.

Norwich proposes that a POSA would know how to use the dosage information for d-amphetamine in the PDR to determine the equivalent dosage to use when administering LDX. Supported by the testimony of Dr. Kaye, Norwich contends that "a POSA would have been motivated and reasonably expected to successfully prescribe a pharmaceutical composition with the recited dosage amount limitations." (Def.'s Br. at 35-36.) Takeda, in opposition, points to the testimony of Dr. McGough, who stated:

> What is the basis for your opinion that a POSA would not have been motivated to administer lisdexamfetamine or lisdexamfetamine dimesylate to treat ADHD?
>
> A. So a POSA would not have been motivated to use an uninvented compound -- an uninvented, unavailable prodrug compound that is untested to treat ADHD.

(Tr. 476:2-7.) Dr. McGough proceeded to explain that a POSA, lacking efficacy and safety data from testing of the prodrug compound, would not have been motivated to administer the compound to humans. (Tr. 476:8-477:2; 480:10-18.)

The Court has weighed the testimony of Dr. Kaye and Dr. McGough and finds Dr. McGough's testimony to be far more persuasive. The Court is not persuaded that, absent safety

and efficacy testing, a POSA would have been motivated to administer an untested chemical compound to a human, nor that a POSA would have a reasonable expectation of success in doing so. In the absence of safety and efficacy data on a new chemical entity, a POSA would not have "reasonably expected to successfully prescribe a pharmaceutical composition with the recited dosage amount limitations." (Def.'s Br. at 35-36.)

3. Inherency

As to the claim limitations involving pharmacokinetic parameters and treatment of illness, Norwich contends that these are obvious based on inherency. Norwich argues that all claim limitations which recite the effects of administration of the LDX prodrug in a human merely claim the natural results of administration of LDX, which are inherent to the compound, citing the Federal Circuit's decision in Santarus:

> The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. To hold otherwise would allow any formulation — no matter how obvious — to become patentable merely by testing and claiming an inherent property.

Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012) (citation omitted). Norwich argues: "there is no dispute that the PK Limitations are simply the result of administering LDX." (Def.'s Br. at 36.) Takeda does not agree. Takeda argues that Defendant's 30(b)(6) designee, Dr. Fackler, stated that the pharmacokinetic parameters were not inherent to LDX:

> Q. Would that lead you to believe that the formulation could play a role in the Cmax of a lisdexamfetamine formulation?
>
> A. Yes.

> Q. And likewise, the formulation could also play a role with respect to the AUC of a lisdexamfetamine dimesylate formulation?
>
> A. Yes, I believe so.
>
> Q. In other words, the pharmacokinetic parameters aren't determined based solely on the active ingredient, lisdexamfetamine dimesylate?
>
> A. That's correct.
>
> Q. Pharmacokinetic parameters aren't inherent to lisdexamfetamine dimesylate, correct?
>
> A. Not C_{max} and AUC.

(Tr. 569:24-570:12.) Norwich is bound by the factual assertions of its 30(b)(6) witness. The Court determines that the formulation plays a role in the *in vivo* functionality of the prodrug, and that characteristics of the *in vivo* functionality of the prodrug are not inherent to the LDX compound itself. This alone defeats Defendant's inherency argument. Furthermore, both Dr. Taft and Dr. Banakar agreed that pharmacokinetics can be affected by factors other than the active ingredient.[16] (Tr. 396:13-16; 771:18-772:10.)

In support, Takeda cites Persion:

> Inherency may not be established by probabilities or possibilities, and the mere fact that a certain thing may result from a given set of circumstances is not sufficient. Rather, inherency renders a claimed limitation obvious only if the limitation is "necessarily present," or is "the natural result of the combination of elements explicitly disclosed by the prior art."

Persion Pharm. LLC v. Alvogen Malta Operations LTD., 945 F.3d 1184, 1191 (Fed. Cir. 2019)

[16] As Dr. Taft observed, the use of an enteric coating in a formulation is an example of how the formulation, independent of the active, can change PK characteristics. (Tr. 779:1-16.) Dr. Taft also stated that a formulator could create an LDX formulation with a T_{max} that did not fall within the scope of the claim limitations. (Tr. 779:24-780:9.) T_{max} therefore cannot be an inherent property of LDX.

(citations omitted.) Dr. Fackler stated that the formulation affects the *in vivo* pharmacokinetic characteristics which therefore cannot be "necessarily present" in the LDX compound itself. Norwich has not proven that any claims reciting limitations related to the *in vivo* prodrug functionality merely claim effects of administration inherent in the compound LDX. Norwich has not proven that a POSA would have had a reasonable expectation of success in obtaining any limitations related to the *in vivo* prodrug functionality of LDX. Norwich has failed to prove that any claims reciting limitations related to the *in vivo* prodrug functionality of LDX are obvious.

F. Obviousness: secondary considerations

Takeda contends that a number of secondary considerations support the non-obviousness of the asserted claims. There is no dispute that Vyvanse® is the commercial embodiment of the asserted claims.

Takeda first contends that Vyvanse® has been a commercial success, citing Dr. Mody's unrebutted testimony that multiple economic indicators demonstrate the commercial success of Vyvanse®. (Tr. 694-706.) Dr. Mody stated that the evidence supported Ms. Whitehouse's characterization of Vyvanse® as a "blockbuster." (Tr. 699:21-700:12.) Norwich conducted a brief cross-examination of Dr. Mody which did not challenge any of her statements. (Tr. 705-706.) In opposition, Norwich argues only that Vyvanse® has continually been outsold by Adderall XR and its generic equivalents, which this Court considers irrelevant to the question of the commercial success of Vyvanse®. Vyvanse® has been a commercial success.

Takeda next contends that Vyvanse® satisfied a long-felt but unmet need, "by virtue of its reduced abuse potential, longer duration of effect, and reduced pharmacokinetic variability." (Pls.' Br. at 33.) As evidence of the reduced abuse potential, Takeda points to two studies

which, as Norwich points out, at best suggest a modest reduction in abuse potential, and none at the highest oral dose of LDX.[17] (Tr. 494:4-9; PTX-660; PTX-657.) While the intravenous study did show that users did not like Vyvanse® but did like d-amphetamine, this is suggestive but insufficient to demonstrate that Vyvanse® has met a long-felt but unmet need.

In opposition to the element of reduced abused potential, Norwich contends not that reduced abused potential is incorrect, but is "overstated." (Def.'s Br. at 46.) In regard to Takeda's contention that Vyvanse® has reduced abuse potential, Norwich points to the undisputed facts that Vyvanse® is a Schedule II drug, which means it has a high potential for abuse, and Vyvanse® also has a black box warning, like other amphetamines. Dr. Kaye also said Vyvanse can be abused, and one way is by simply taking a higher dose. (Tr. 835:8-13.) Viewed as a whole, the evidence is insufficient to demonstrate that Vyvanse® has met a long-felt but unmet need for an ADHD treatment with reduced abuse potential.

As to duration, Takeda contends that prior art treatments for ADHD were effective up to 12 hours, but one study of Vyvanse® (PTX-684) showed efficacy in children up to 13 hours, and another study (PTX-685) showed efficacy in adults up to 14 hours. Takeda argues that this shows satisfaction of a long-felt but unmet need, but the Court is not persuaded that there was a long-felt but unmet need for an extra hour or two of efficacy beyond twelve hours. Takeda does not even attempt to demonstrate that there was a long-felt but unmet need for an extra hour or two. Also, as Norwich points out, the cited studies did not compare Vyvanse® to other medications, and the available literature has not demonstrated a clinically significant difference

[17] The abstract for the oral study states that the subjects liked a dose of 40 mg of d-amphetamine as much as they liked a dose of 150 mg of LDX. (PTX-660.) Dr. Kaye noted this as well. (Tr. 834:13-17.)

between the duration of action of the various long-acting treatments. Norwich points out that the Cochrane study concluded that there is no proven difference in efficacy among amphetamine derivative treatments; both Drs. McGough and Kaye affirmed this. (Tr. 539:15-22; 839:18-24.) The evidence is insufficient to demonstrate that Vyvanse® has met a long-felt but unmet need for an ADHD treatment with an extra hour or two of efficacy.

Third, Takeda contends that Vyvanse® met a long-felt but unmet need for an ADHD treatment with reduced pharmacokinetic variability. Takeda cites the testimony of Dr. McGough, who described a study (DTX-381) on Adderall XR and a study (PTX-689) of both Vyvanse® and Adderall XR. Dr. McGough stated that the second study showed "much lower interpatient variability in terms of the pharmacokinetic parameters compared to Adderall." (Tr. 509:24-510:1.) Norwich did not oppose this point, but the Court again finds that the evidence is unpersuasive. What does "lower interpatient variability" mean, and what is the evidence that there was a long-felt but unmet need for it? Who had this need and what was the problem? What is the evidence that the lower interpatient variability of Vyvanse® is sufficient to meet the unmet need? Dr. Kaye stated: "The low PK variability of Vyvanse® is not clinically relevant and did not meet a long-felt need. (Tr. 842:6-21.) Dr. Kaye's testimony on this point is persuasive, if only because Takeda did not even try to demonstrate the clinical relevance of lower interpatient variability. The evidence is insufficient to demonstrate that Vyvanse® has met a long-felt but unmet need for an ADHD treatment with lower interpatient variability.

Takeda also contends that Vyvanse® exhibited unexpected results. The Federal Circuit has held:

> In considering unexpected results, courts ask whether the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the

> relevant art would have found surprising or unexpected. . . . [T]he results must be unexpected by one of ordinary skill in the art at the time of the application.

Forest Labs., LLC v. Sigmapharm Labs., LLC, 918 F.3d 928, 937 (Fed. Cir. 2019) (citations omitted). Forest teaches that courts ask first whether the invention exhibits a superior property or advantage. In short, the Court is not persuaded that the unexpected results Takeda identifies are superior properties or advantages that are supported by the evidence. Takeda offers this list: "reduced abuse potential compared to d-amphetamine . . ., a longer duration of effect, an optimal extended release profile, and larger effect sizes compared to other ADHD medications." As already discussed with regard to Takeda's evidence about longer duration of effect, the only study Takeda cited that compared Vyvanse® to Adderall XR showed that the duration of effect was the same. As already discussed, the experts agreed that the Cochrane study concluded that no differences in efficacy among stimulant treatments for ADHD have been proven. As to reduced abuse potential, Takeda cites the Ermer study, but that study states: "It should be noted that assessing the abuse liability of the two regimens was not an objective of the current study . . . This limits the interpretation of the data in terms of abuse liability." (PTX-674 at 368.) Similarly, the Court is not persuaded that the opposite hysteresis loop is a superior property. As for the results of the kitchen and garage tests, the evidence suggests finding that Vyvanse® exhibits a superior property, although Takeda provides no basis for comparison to other amphetamine treatments, but Takeda omits evidence that a POSA at the time of application would not have expected these results, as Norwich notes. Takeda's statement of the law of unexpected results in PFOF ⁋ 669 is quite different from that stated by the Federal Circuit in Forest.

Takeda next contends that Vyvanse® has received industry praise. Takeda's principal

example of industry praise is the 2011 Medical Letter, a short just-the-facts paragraph that is faint praise, if that, as it notes similar efficacy to other amphetamines, just as the Cochrane review did. (PTX-707 at 25.) The paragraph also states: "Lisdexamfetamine has no euphoric effects if given IV or taken intranasally and is thought to have less potential for abuse than amphetamine itself." (Id.) The phrase, "is thought to have less potential for abuse," is true faint praise and suggests both subjective opinion and an absence of empirical support.

Takeda contends that Defendant's ANDA application is evidence of copying and supports an inference of nonobviousness. The Federal Circuit rejected a similar argument about copying in the ANDA context: "Such evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013). Takeda cites Heidelberger in support, contending that Norwich "tried and failed to solve the same problem, and then promptly adopted the solution that they are now denigrating." Heidelberger Druckmaschinen AG v. Hantscho Commer. Prods., 21 F.3d 1068, 1072 (Fed. Cir. 1994). This is not the same story Plaintiffs' counsel told in Court about Norwich:

> And then they changed their mind, they did a salt study that was not successful, they tried to design around, if you will, they couldn't do it. So then they switched from a P3 to P4 and that's how we got into this case.

(Tr. 545:23-546:1.) These facts suggest that the salt selection was copied after failure to find an alternative salt outside the scope of the patents, and thus is evidence that the mesylate salt limitation is non-obvious, but not more than that.

The Court finds that Takeda has demonstrated that the secondary consideration of commercial success, and copying of the selection of the dimesylate salt, supports a finding of

non-obviousness.

Considering all the evidence and arguments regarding the obviousness of the claims at issue, including evidence of secondary considerations, the Court concludes that Norwich has failed to prove, by clear and convincing evidence, that the asserted claims are invalid as obvious.

II. The '770 patent

Norwich argues that claim 10 of the '770 patent is anticipated by or obvious over the '955 publication. The '770 patent states that it stems from application no. 12/201,739, which was a continuation of application no. 11/400,304, filed on April 10, 2006. The '955 publication states that it is the publication of application no. 11/400,304, filed on April 10, 2006. Norwich's argument about the invalidity of claim 10 is thus premised on the question of whether claim 10 of the '770 patent is entitled to the priority date of application no. 11/400,304. If it is entitled to that priority date, the '955 publication is not prior art.

Norwich argues that claim 10 cannot claim priority to the '304 application because that application lacks adequate written description of the genus of pharmaceutically acceptable salts, as recited by claim 10. The parties agree that "[f]or a claim to effectively claim earlier priority, the earlier application must satisfy the written description and enablement requirements for that claim." (Pls.' Br. at 40.) Given the presumption of patent validity stated in 35 U.S.C. § 282, Norwich bears the burden of proof that the requirements for the claim of a Priority Date of April 10, 2006 have not been satisfied. Norwich relies on Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1350 (Fed. Cir. 2010), which states:

> We held that a sufficient description of a genus instead requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus. *Id*. at 1568-69. We

> explained that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.

Takeda's post-trial brief does not address the issue of written description support for the genus of pharmaceutically acceptable salts, and this Court can see why it does not: the argument was not raised or disclosed in Defendant's pre-trial brief nor in the Final Pretrial Order. The FPTO contains a summary of the invalidity defenses for each claim at issue, including claim 10 of the '770 patent, and does not mention the defense of lack of written description. (FPTO at 15.) The FPTO does state an invalidity defense of lack of written description for claim 5 of the '770 patent, to be supported by the testimony of Dr. Kaye. (FPTO at 14.) Consistent with this, Defendant's pre-trial brief discloses the argument that claim 5 of the '770 patent lacks adequate written description: "However, no application that the '770 patent claims priority to filed before January 6, 2006 discloses treatment in such subjects, what doses would be effective, how they should be administered, or how to ascertain whether the treatment was successful." (Def.'s Pre-Trial Br. at 26.) In short, Norwich did not timely disclose the argument that claim 10 of the '770 patent lacks adequate written description of the genus of pharmaceutically effective salts.[18] Defendant's assertion of this new argument in its post-trial brief was untimely and has prejudiced Plaintiffs, and the Court will not consider it.

III. Invalidity due to lack of enablement

Norwich asserts that the various salt limitations are not enabled, but the argument is raised as a contingent argument. Norwich offers a few different versions of the contingency that

[18] In fact, the argument in Defendant's pre-trial brief about claim 5 does not mention any argument about written description support for the genus of pharmaceutically acceptable salts.

must be satisfied to trigger the non-enablement argument. In its pre-trial brief, Norwich asserted, for example:

> Thus, to the extent Takeda alleges that salt formation is unpredictable and complex, the '526 application does not provide sufficient information for a POSA to make and use the claimed LDX dimesylate salts without undue experimentation.
>
> For at least these reasons, the '526 application did not provide a disclosure that would enable a POSA to make and use the claimed dimesylate salts of LDX without undue experimentation. Therefore, claim 1 of the '630 patent, claim 7 of the '031 patent, claim 5 of the '770 patent, and claims 4 and 25 of the '030 patent, are invalid as lacking an enabling disclosure unless they are invalid as obvious.

(Def.'s Pre-Trial Br. at 40.) This states two different contingencies, the first contingent on "the extent Takeda alleges that salt formation is unpredictable and complex," the second contingent on whether the claims are determined to be invalid as obvious. The post-trial brief asserts a different version of the contingency: "But if the Court were to somehow credit Dr. Chyall's opinions on obviousness, then the eleven Non-Enabled Claims reciting the 'dimesylate,' 'mesylate,' and 'pharmaceutically acceptable' salt limitations are invalid for lack of enablement." (Def.'s Br. at 52.) The Court declines to sort through these different contingencies, and will go right to Defendant's non-enablement argument.

Unfortunately, Norwich fares no better with explaining the non-enablement argument. One part of this is a legal argument, which raises the purely legal question of whether, under Federal Circuit law, enablement is determined based on the claims and specification of the issued patent, or a combination of the issued claims and the specification of the application with the earliest priority date relied on by the issued patent. Norwich argues that the Court should determine enablement based on the disclosures in the earliest application, not those in the issued patent. In support, Norwich cites two cases, Biogen and Janssen, but offers no discussion or

analysis of these cases to explain the argument. Biogen deals with the written description requirement, not the enablement requirement. Biogen Int'l GmbH v. Mylan Pharm., Inc., 18 F.4th 1333, 1342 (Fed. Cir. 2021). Janssen does deal with the enablement requirement, but Norwich has not explained how Janssen supports its position on enablement, nor is it apparent to the Court. Janssen Pharmaceutica N.V. v. Teva Pharm. USA, Inc. (In re '318 Patent Infringement Litig.), 583 F.3d 1317, 1323-24 (Fed. Cir. 2009). Norwich has not sufficiently explained its legal argument for the Court to cognize it and decide it.

Lastly, there is the evidence. The Court has already determined the key facts related to enablement of the salt claims. Methods of salt selection and salt formation were well known in the art. To the extent that Norwich relies on the testimony of Dr. Sloan – the putative expert on salt selection who never did one – the Court determined that Dr. Sloan's testimony will be given no weight. Defendant's enablement argument concerns the knowledge to make and use salt forms.

The Court understands Defendant's enablement argument to rely on the contention that various disclosures do not enable the full scope of all the salt claims. The Federal Circuit has held:

> [T]he specification must enable the full scope of the claimed invention. . . This is not to say that the specification must expressly spell out every possible iteration of every claim. For instance, a specification need not disclose what is well known in the art.

Trs. of Bos. Univ. v. Everlight Elecs. Co., 896 F.3d 1357, 1364 (Fed. Cir. 2018). The Court has already determined that methods of salt formation were well known in the art. A specification need not disclose what is well known in the art. Norwich has failed to prove, by clear and convincing evidence, that the salt claims are invalid for lack of enablement.

CONCLUSION

The Court concludes that Norwich has failed to prove, by clear and convincing evidence, that claims 1 and 4 of the '630 patent, claim 2 of the '787 patent, claim 14 of the '466 patent, claim 4 of the '486 patent, claims 5 and 10 of the '770 patent, claim 7 of the '031 patent, claim 12 of the '735 patent, claims 1, 6, and 9 of the '561 patent, and claims 4 and 25 of the '030 patent are invalid under its theories based on § 103 obviousness, § 102 anticipation, or the enablement requirement stated in 35 U.S.C. § 112 ¶ 1. This Court determines that all asserted claims are valid and enforceable. The parties have stipulated to infringement, and the Court determines that Norwich has infringed every claim at issue. Judgment will be entered in favor of Plaintiffs on their infringement claims and on Defendant's affirmative defenses and counterclaims.

Pursuant to FED. R. CIV. P. 52(a), the Court presents its findings of fact and conclusions of law.

FINDINGS OF FACT

I. This Opinion incorporates by reference all stipulated facts set forth in the Final Pretrial Order.

II. Based on the evidence presented at trial, this Court now makes the following findings of fact:

1. L-lysine-d-amphetamine dimesylate is a prodrug of d-amphetamine. That is, it is biologically inactive until it is converted in the body to d-amphetamine.

2. The Court takes judicial notice of the Orange Book listing for Vyvanse®, which states that all listed patents expire on 2/24/2023, with a date of 8/24/2023 reflecting the Pediatric Exclusivity period. "Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations," https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=007

&Appl_No=021977&Appl_type=N (last visited 12/26/2022).

3. The parties have agreed to the following Priority Dates: claim 12 of the '735 patent – May 29, 2003; claim 1 of the '630 patent, claims 4 and 25 of the '030 patent, claim 4 of the '486 patent, claim 7 of the '031 patent, and claim 5 of the '770 patent – June 1st, 2004; and claim 4 of the '630 patent, claim 14 of the '466 patent, and claims 1, 6 and 9 of the '561 patent – January 6th, 2006.

4. As of the Priority Dates for the patents in suit, d-amphetamine was a known, effective treatment for ADHD and that the abusability of d-amphetamine was a known problem, as reflected in the PDR black box warning. The POSA would have identified the abusability problem of d-amphetamine as the problem to be solved. LDX was unknown.

5. A POSA would have known that d-amphetamine drugs were commonly abused by crushing the tablets and then snorting or injecting the resulting powder ("the d-amphetamine abuse problem.") The d-amphetamine abuse problem was the problem to be solved.

6. A POSA seeking to solve the d-amphetamine abuse problem would have had a reason to select d-amphetamine as the lead compound.

7. A POSA would have believed that: 1) euphoria is an effect of administration of d-amphetamine; 2) euphoria results from initial spiking in the plasma concentration curve of d-amphetamine; 3) the euphoric effect of d-amphetamine can lead to the d-amphetamine abuse problem; and 4) a prodrug can change the plasma concentration curve of a drug to reduce initial spiking.

8. A POSA would have been motivated to take some action to minimize the euphoric effect of d-amphetamine to reduce d-amphetamine's abuse potential. A POSA would have been motivated to create a d-amphetamine product with sustained-release characteristics in order to minimize initial spiking in the plasma concentration curve of d-amphetamine.

9. The art taught various techniques for reducing initial spiking in the plasma concentration curve of a drug, including formation of a prodrug, as well as formulation-based approaches to changing the plasma concentration curve. The art also taught formulation-based techniques to resist crushing of tablets, to deter abuse, and to deter abuse of an extended-release formulation. The art taught various techniques to create a sustained-release formulation.

10. The art did not teach that crushing tablets of prodrugs would have no impact on the *in vivo* functionality or performance of the prodrug. Absent testing, a POSA could not predict the impact of tablet crushing on an amide bond in a prodrug.

11. The DEA Brochure did not teach that the crushing of an extended release formulation defeats the extended release technology that was intended to sequester or moderate release of the drug.

12. The art did not teach that the prodrug form of a drug would provide additional abuse-deterrent properties beyond the potential impact on the plasma concentration curve.

13. A prodrug has the potential to have varied impacts on the *in vivo* functionality and performance of the active drug. Among various possible impacts, the prodrug form may increase or decrease the T_{max} or the C_{max} of the plasma concentration curve of the active, or the promoiety may fail to cleave in the body and fail to release the active ingredient, or the prodrug itself may not be biologically inactive in the body.

14. Absent testing, a POSA cannot predict the *in vivo* functionality or performance of a prodrug, nor the characteristics of the resultant plasma concentration curve of the active drug if released. Absent testing, a POSA cannot predict the *in vivo* PK characteristics of any particular prodrug.

15. Adderall XR is an extended-release amphetamine formulation that manifested increased abuse liability in regard to crushing, snorting, and injection. The art did not conclude from this that no abuse-deterrent extended-release amphetamine formulations were possible or that a formulation-based approach to an abuse-deterrent extended-release amphetamine product could not succeed.

16. A POSA could have reasonably believed that the success of a prodrug approach to an abuse-resistant amphetamine product was more uncertain than a formulation-based approach.

17. The LDZ example in the Patrick reference did not teach a method of synthesis of the prodrug.

18. The LDZ example in the Patrick reference teaches a modification of a chemical precursor to the active drug of interest, not modification of the active drug itself. Norwich did not identify a precursor to d-amphetamine to modify in the same way that Patrick modified the precursor in that example. The Patrick reference teaches that the final product after the prodrug is cleaved *in vivo* is not the active drug of interest, but instead must undergo further transformation, cyclization, in the body. D-amphetamine cannot cyclize.

19. A POSA would not believe that d-amphetamine can be simply swapped with diazepam in the LDZ example in Patrick and that LDX would result. Norwich

did not explain the steps that would be required for a POSA to adapt the method of the LDZ example to d-amphetamine, nor the choice points in the adaptation process and the reasons for making certain choices, that would result in LDX. Norwich did not explain how a POSA would apply the teachings of the LDZ example in Patrick to achieve LDX.

20. Example 5 in Miller contains a mistake that Dr. Mallamo did not perceive. Dr. Mallamo incorrectly believed that Example 5 taught a prodrug of metaraminol with a promoiety of l-lysine. A POSA would have perceived the mistake and would have understood that Example 5 teaches a prodrug that does not have a promoiety of l-lysine.

21. Formula II in the Miller reference states an express preference for acylated amino acids; l-lysine is not an acylated amino acid.

22. Salt forms of pharmaceutical compounds are common, and chemical reactions that result in salt forms of pharmaceutical compounds are common and well known in the art of pharmaceutical development. The reactions which form salts are well known and a POSA can predict whether a particular reaction will occur, but cannot predict the properties of the resultant salt. A POSA could not predict whether the resultant salt would be sufficiently stable to make that salt pharmaceutically acceptable.

23. The Cavallito reference states: "Examples abound of chemically similar compounds with markedly different pharmacological properties and dissimilar chemicals with comparable pharmacology." A POSA would have believed this to be correct. A POSA would not believe that pharmaceutical compounds with structural similarities can be reasonably expected to function similarly *in vivo*.

24. Absent safety and efficacy testing, a POSA would not have been motivated to administer an untested chemical compound to a human, nor would a POSA have a reasonable expectation that the compound would work for its intended purpose.

25. The *in vivo* PK characteristics of a prodrug formulation are not solely a function of the active ingredient; the formulation itself, apart from the active ingredient, affects *in vivo* PK characteristics.

26. Vyvanse® has been a commercial success. Vyvanse® has not satisfied any long-felt but unmet needs. Vyvanse® has not exhibited any superior properties which have been demonstrated to be unexpected results. Vyvanse® has not received notable industry praise. Norwich copied Takeda's choice of salt, the dimesylate, but not LDX itself, within the meaning of the law of secondary considerations.

27. In the FPTO and in its pre-trial brief, Norwich did not disclose the argument that

claim 10 cannot claim priority to the '304 application because that application lacks adequate written description of the genus of pharmaceutically acceptable salts.

CONCLUSIONS OF LAW

17. This Court has jurisdiction over this case pursuant to 28 U.S.C. § 1331.

18. The parties accept this Court's personal jurisdiction.

19. Venue is proper in this district pursuant to 28 U.S.C. § 1391(b).

20. Takeda asserts infringement of claims 1 and 4 of the '630 patent, claim 2 of the '787 patent, claim 14 of the '466 patent, claim 4 of the '486 patent, claims 5 and 10 of the '770 patent, claim 7 of the '031 patent, claim 12 of the '735 patent, claims 1, 6, and 9 of the '561 patent, and claims 4 and 25 of the '030 patent.

21. "A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282.

22. "Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1360 (Fed. Cir. 2011) (citation omitted).

23. Under Federal Circuit law, the lead compound analysis has two steps: "Our case law demonstrates that whether a new chemical compound would have been prima facie obvious over particular prior art compounds ordinarily follows a two-part inquiry. First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts. . . . The second inquiry in the analysis is whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1291-92 (Fed. Cir. 2012).

24. A POSA would have selected d-amphetamine as a lead compound when attempting to solve the d-amphetamine abuse problem. Norwich failed to prove, by clear and convincing evidence, that a POSA would have been motivated to combine the d-amphetamine abuse problem with a prodrug solution. Norwich failed to prove, by clear and convincing evidence, that a POSA would have been motivated to modify the lead compound, d-amphetamine, to create a prodrug to improve the d-amphetamine abuse problem, nor that a POSA would have had a reasonable expectation of success in doing so.

25. Norwich failed to prove that use of an l-lysine promoiety to create a d-amphetamine prodrug was an identified, predictable solution that was obvious to try.

26. Norwich failed to prove, by clear and convincing evidence, that a POSA would have been motivated to combine the LDZ example in the Patrick reference with the d-amphetamine abuse problem, nor that a POSA would have had a reasonable expectation of success in arriving at LDX.

27. Norwich failed to prove, by clear and convincing evidence, that a POSA would have been motivated to combine the Miller reference with the d-amphetamine abuse problem, nor that a POSA would have had a reasonable expectation of success in arriving at LDX.

28. All asserted claims require the compound LDX. Because Norwich has failed to prove that claim 2 of the '787 patent, requiring only the compound LDX, is obvious, it cannot prove that any of the remaining claims is obvious.

29. Norwich failed to prove, by clear and convincing evidence, that a POSA would have been motivated to select l-lysine as the promoiety in a d-amphetamine prodrug, nor that a POSA would have had a reasonable expectation that LDX would work for its intended purpose.

30. Norwich failed to prove, by clear and convincing evidence, that a POSA would have had a reasonable expectation of success in forming a specific pharmaceutically acceptable salt.

31. Norwich failed to prove, by clear and convincing evidence, that a POSA would have had a reasonable expectation of success in creating a prodrug with any of the *in vivo* functional limitations in the asserted claims.

32. A formulation does not "become patentable merely by testing and claiming an inherent property." Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed.

Cir. 2012). "[I]nherency renders a claimed limitation obvious only if the limitation is 'necessarily present.'" Persion Pharm. LLC v. Alvogen Malta Operations LTD., 945 F.3d 1184, 1191 (Fed. Cir. 2019).

33. Norwich has not demonstrated that the PK parameters that appear as claim limitations in the asserted patents are necessarily present in every covered pharmaceutical composition as recited in those claims. Norwich has not demonstrated that the PK parameters that appear as claim limitations in the asserted patents are inherent properties of LDX.

34. Having considered all of the evidence of record, the Court concludes that Norwich failed to prove, by clear and convincing evidence, that the asserted claims are invalid as obvious.

35. Defendant's assertion of the argument that claim 10 cannot claim priority to the '304 application because that application lacks adequate written description of the genus of pharmaceutically acceptable salts is untimely and its assertion after trial has prejudiced Plaintiffs. That argument will not be considered.

36. The Court declines to reconcile the variations in Defendant's formulation of the contingency which triggers its non-enablement argument and treats the contingency as satisfied and the argument asserted. Norwich has not sufficiently explained the application of Janssen as controlling authority in support of this argument.

37. "[A] specification need not disclose what is well known in the art." Trs. of Bos. Univ. v. Everlight Elecs. Co., 896 F.3d 1357, 1364 (Fed. Cir. 2018). Defendant has no evidence of non-enablement. Norwich failed to prove, by clear and convincing evidence, that the asserted claims are invalid for lack of enablement.

38. Norwich has failed to prove, by clear and convincing evidence, that claims 1 and 4 of the '630 patent, claim 2 of the '787 patent, claim 14 of the '466 patent, claim 4 of the '486 patent, claims 5 and 10 of the '770 patent, claim 7 of the '031 patent, claim 12 of the '735 patent, claims 1, 6, and 9 of the '561 patent, and claims 4 and 25 of the '030 patent are invalid under its theories based on § 103 obviousness, § 102 anticipation, or the enablement requirement stated in 35 U.S.C. § 112 ¶ 1.

39. All claims at issue in this case are valid and enforceable.

40. This Court honors and enforces the stipulation entered into by the parties, in which Norwich agreed to a determination of infringement for the claims at issue. In filing the ANDA applications at issue, Norwich infringed the claims at issue.

41. By filing ANDA No. 214547, Norwich has infringed the following valid and enforceable claims: claims 1 and 4 of the '630 patent, claim 2 of the '787 patent, claim 14 of the '466 patent, claim 4 of the '486 patent, claims 5 and 10 of the '770 patent, claim 7 of the '031 patent, claim 12 of the '735 patent, claims 1, 6, and 9 of the '561 patent, and claims 4 and 25 of the '030 patent.

42. This judgment of infringement entitles Takeda to the following relief: "[T]he court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. § 271(e)(4)(A). When the infringer has filed a Paragraph IV certification with its ANDA, the NDA holder is entitled to an Order which reflects the six-month Pediatric Exclusivity period extension. In re Omeprazole Patent Litig. v. Apotex Corp., 536 F.3d 1361, 1368 (Fed. Cir. 2008). The Orange Book lists a six-month Pediatric Exclusivity period extension for every asserted patent. Takeda is entitled to an Order stating that the effective date of any approval of ANDA No. 214547 shall be no earlier than 8/24/2023.

An appropriate Order follows.

s/ Stanley R. Chesler
Stanley R. Chesler, U.S.D.J.

Dated: December 27, 2022